

CLINICAL INVESTIGATION

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

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Editor's key points

- Perioperative anaphylaxis is a rare but life-threatening condition that may have geographical differences in incidence.
- Data on severe perioperative anaphylaxis were collected from 112 tertiary care hospitals from seven regions of mainland China.
- A total of 447 cases out of 5 078 118 surgical procedures over 12 months met inclusion criteria, leading to an incidence of suspected perioperative anaphylaxis of one in 11 360 anaesthetics, similar to previous estimates.
- Differences between the southern and northern regions of China by geographic location may be attributable to genomic differences, which will require further investigation.

Perioperative anaphylaxis can be life-threatening, leading to prolonged hospitalisation and death.¹ 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.^{2,3} 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.³

The recent publication by Harper and colleagues⁴ 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.^{4–6} 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.^{4,7}

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.^{8,9} 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.^{10,11} 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.¹²

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.^{13,14} Investigators have been able to trace populations with high gene frequencies to a common ancestry that is often identified through migration patterns.¹⁵ Genomic analysis has shown significant differences between the north and south of China that were traced to migration routes created by the Yangtze River.¹⁵ Information about genome associated migration ancestry within China helped 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.¹⁶

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.¹⁷

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.¹⁸ 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.¹⁹ 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.¹⁸ 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.^{2,20}

Anaphylaxis was defined using published guidelines.²¹ 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 ultrasonography. 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.¹⁸ 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

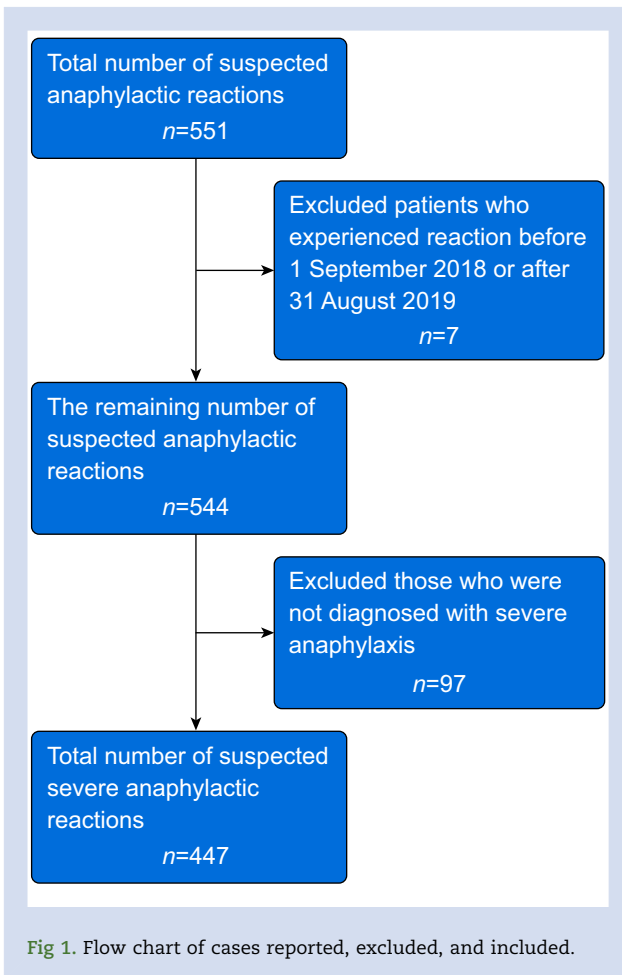
The EpiData 3.1 (Odense, Denmark) statistical software package was used for database design and data entry. Two data entry clerks who were blinded to the study objective input patient data. Accuracy was checked via visual inspection of the database and examination of data for unexplained outliers.

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 χ^2 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



sites was one in 11 360 procedures (95% confidence interval [CI], from 1:10 397 to 1:12 521).

The median age of patients was 53 yr (IQR, 35–64 yr). Most affected patients received general anaesthesia (Table 1). We randomly sampled 86 of the 112 centres to measure the male/female ratio in incidence for all surgeries during the study period, which was 1.70 ($P < 0.01$).

Incidence of suspected perioperative anaphylaxis by geographical region

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 1:11 698 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 19 262 (95% CI, from 1:33 088 to 1:13 585), one in 14 785 (95% CI, from 1:20 232 to 1:11 703), and one in 13 319 (95% CI, from 1:20 381 to 1:9892), respectively. Central China and East China had intermediate rates of one in 13 265 (95% CI, from 1:17 810 to 1:10 568) and one in 11 059 (95% CI, from 1:13 001 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 μ g (IQR, 20–265 μ g). Far fewer of the 447 patients ($n=151$; 33.8%) received norepinephrine, and it was the first choice of treatment in only 36.4% ($n=55$) 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

Table 1 Patient characteristics. IQR, inter-quartile range.

	n (%)
Total patients	447
Sex	
Male	227 (50.8)
Female	220 (49.2)
Median age, yr (IQR)	53 (35–64)
BMI, kg m ⁻²	
Normal	188 (42.1)
Overweight	123 (27.5)
Obese	44 (9.8)
Ethnic group	
Han nationality	425 (95.1)
Minority nationalities	22 (4.9)
ASA physical status	
1	41 (9.2)
2	281 (62.9)
3	107 (23.9)
4	18 (4.0)
Anaesthesia type	
General anaesthesia	414 (92.6)
Spinal anaesthesia	11 (2.5)
Local anaesthesia	3 (0.7)
Allergy history	
Drug allergy history	68 (15.2)
Food allergy history	15 (3.4)
Other allergy history	6 (1.3)
Comorbidities	
Cardiovascular disease	133 (29.8)
Respiratory disease	36 (8.1)

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 incidence of reactions varies between these two populations.

The death rate of 2.0% in our population was less than the 3–9% reported in other studies. Reasons for the better outcome in our study cohort are unclear as other investigators reported higher mortality even when similar treatment was administered in a timely manner.²² Similar to the latter study, more non-survivors had underlying cardiovascular disease.

The ratio of incidence in male to female patients was 1.70 ($P<0.01$), which contrasts with a previous report showing a female predominance.⁷ This observation deserves further study in view of the larger number of female surgical patients at the included study sites.⁷ Our study was not designed to address this unexpected observation, but we note similar

ratios for ethnically derived Han populations who migrated from southern China to Singapore.²³ The European Anaphylaxis Registry also reported more males experienced severe anaphylaxis than females such that collecting data about more severe reactions could have increased the number of males represented in this study.²⁴

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.²⁵ A diagnosis may be overlooked in patients with milder symptoms, whereas the use of drugs with direct effects such as flushing²⁵ or hypotension can lead to diagnostic errors.²⁶ 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.⁴ 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.^{27–29} This approach has been shown to be effective and is used in diverse organisational conditions to improve adherence to protocols.³⁰

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.⁹ 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.⁴ 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.^{31–33}

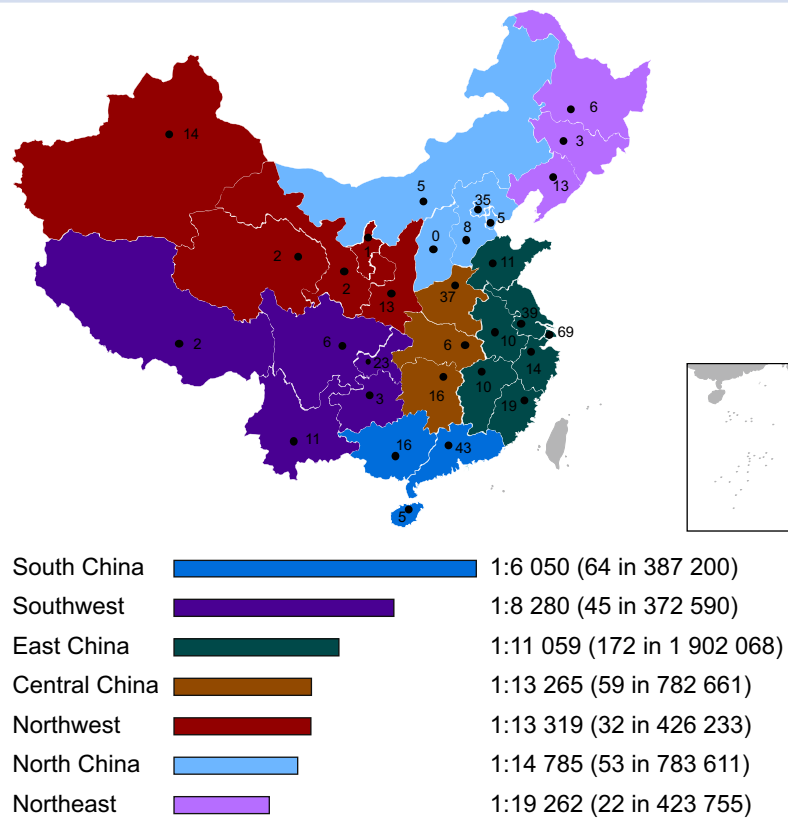


Fig 2. Incidence of suspected life-threatening perioperative anaphylaxis in seven geographical regions of mainland China.

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.

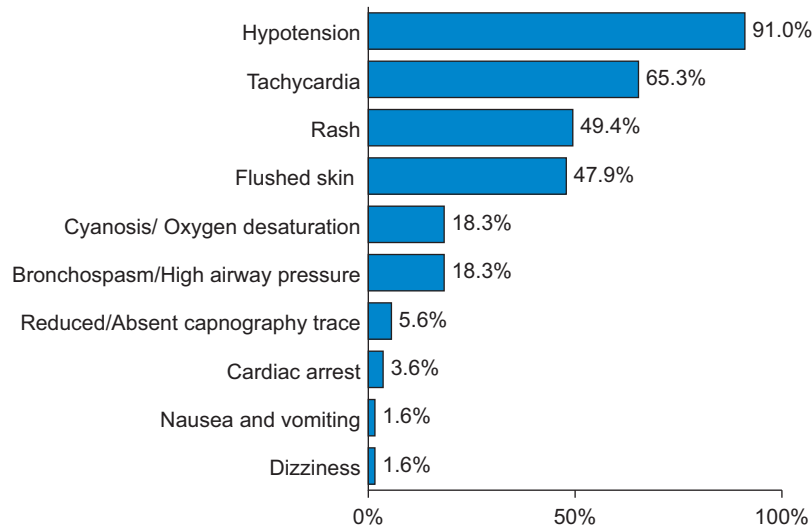


Fig 3. Common presenting features during anaphylactic reactions.

Table 2 Comparison of patients who survived or died after perioperative anaphylaxis. * $P < 0.05$. †Fisher's exact test.

	Died after anaphylaxis n=9 (%)	Survived after anaphylaxis n=438 (%)	P value
Age ≥ 60 yr	5 (55.6)	156 (35.6)	0.29 [†]
ASA physical status ≥ 3	5 (55.6)	120 (27.4)	0.12 [†]
Coronary artery disease	2 (22.2)	14 (3.2)	0.03* [†]
Asthma	0 (0)	4 (0.9)	1.00 [†]
Allergy history	2 (22.2)	77 (17.6)	0.66 [†]

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.³⁴ An example is beta-lactam antibiotic anaphylaxis recently mapped to a single nucleotide polymorphism, of which the HLA-DQA1*01:05 loci is an example.^{10,11,34,35} Other variants at the DBR1 site can be examined for their known role in perioperative radio-iodine contrast and latex anaphylaxis.^{34,35} 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.^{10,11}

We propose protein testing to identify changes in Mas-related G protein-coupled receptor X2 (MRGPRX2) on mast cells, coded by chromosome 11.¹² This is one of the mechanisms where rocuronium, cis-atracurium, remifentanyl, and morphine directly activate a variant receptor causing mast cell degranulation.³⁶ 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.³⁷ 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.³⁸ However,

systematic interventions such as collaborative networking have improved adherence to protocols.³⁹ 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.⁴⁰ 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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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>.

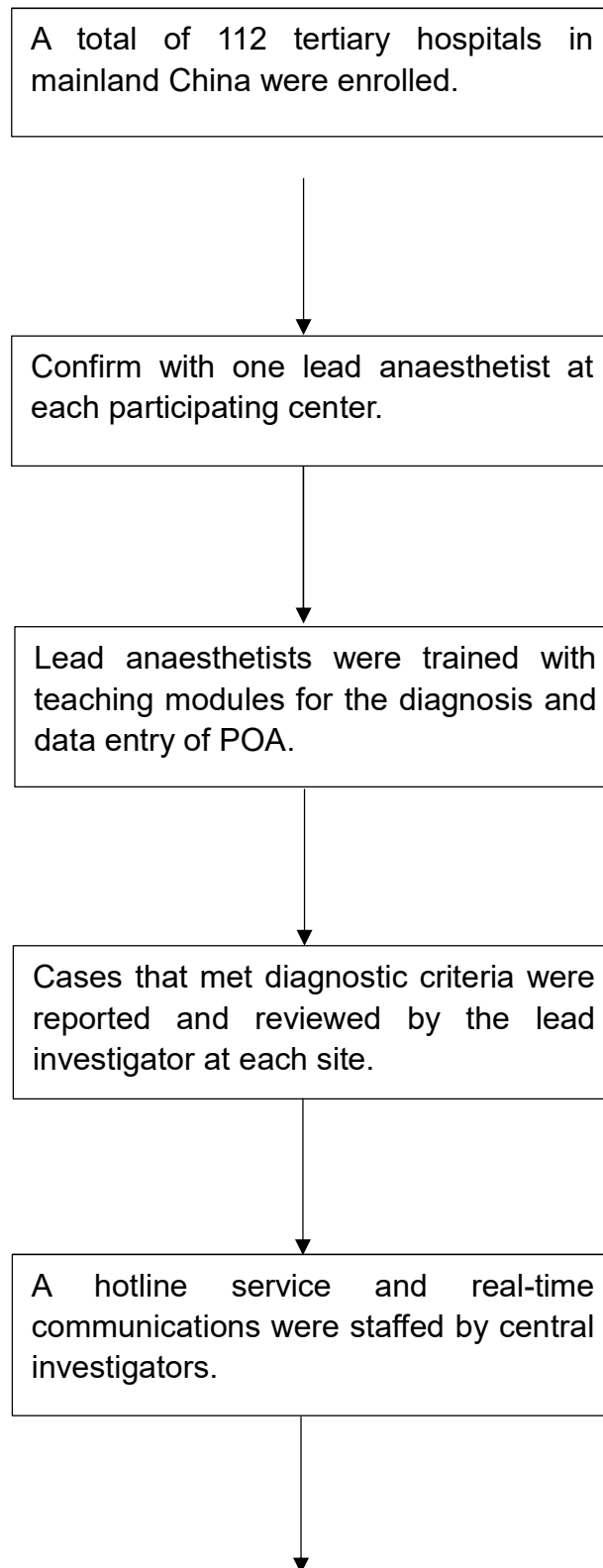
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Supplemental Figure 1. Flowchart of supporting information on how to conduct this study.



The latter investigators had immediate telephone access to specialists in the field of allergy who had experience with POA to address any remaining questions.



Suspected POA cases were submitted to the central team of investigators for a second tier of quality analysis.

Supplemental Table 1. Definitions for clinical terms used in the clinical diagnosis

Clinical term	Definition
Severe hypotension	a fall in systolic blood pressure to <70 mmHg or a decrease of >30% from a previous baseline value during anaesthetic maintenance.
Cardiac arrest	The loss of effective circulation defined as pulseless electrical activity or due to other conduction abnormality and/or a blood pressure < 50 mm Hg systolic
Tachycardia	An increase in heart rate to >100 beat/ min or > 50% from a previously stable value
Cyanosis/oxygen desaturation	SpO ₂ <90%
High airway pressure	an increase of airway peak pressure to > 35 cmH ₂ O or >30% from a previously stable baseline value that is not due to changes in ventilation parameters or other mechanical causes.

(Continued)

Supplemental Table 1. (*Continued*)

Clinical term	Definition
Bronchospasm	The onset of wheeze on auscultation, any manifestation of otherwise unexplained increased airway resistance, or both
Severe bronchospasm	Bronchospasm associated with SpO2 <85%
Urticaria	A skin rash characterized by raised pink or white raised areas of skin(wheals)
Angioedema	Dermal or mucosal swelling

Included in the definition of the signs is that they are not explained by surgical, anesthesia or patient conditions.

Supplemental Table 1. is labeled as an online only supplement.

Supplemental Table 2. Anaesthesia method in China

Regions	The percentage of hospitals with general anaesthesia as the major anaesthesia method(>50%)	The percentage of hospitals with spinal anaesthesia as the major anaesthesia method(>50%)	The incidence of suspected life threatening perioperative anaphylaxis
South China	100.00%	0.00%	1.65/10,000
Southwest	100.00%	0.00%	1.21/10,000
East China	94.50%	8.10%	0.90/10,000
Central China	87.50%	0.00%	0.75/10,000
Northwest	100.00%	0.00%	0.75/10,000
North China	100.00%	4.00%	0.67/10,000
Northeast	100.00%	0.00%	0.52/10,000

Supplemental Table 2. is labeled as an online only supplement.

Supplemental Table 3. The commonly used anaesthetics in China

Regions	The percentage of hospitals with the commonly used inhalation anesthetics	The percentage of hospitals with the commonly used sedative hypnotics				The percentage of hospitals with the commonly used analgesics			The percentage of hospitals with the commonly used muscle relaxants			The incidence of suspected life threatening perioperative anaphylaxis
		Sevoflurane	Propofol	Etomidate	Midazolam	Sufentanil	Remifentanil	Fentanyl	Rocuronium	Cis-atracurium	others	
South China	100.0%	100.0%	75.0%	58.3%	91.6%	91.6%	16.7%	75.0%	100.0%	8.3%	1.65/10,000	
Southwest	100.0%	100.0%	62.5%	75.0%	87.5%	100.0%	37.5%	100.0%	75.0%	25.0%	1.21/10,000	
East China	100.0%	97.3%	70.3%	78.4%	97.3%	86.5%	32.4%	86.5%	83.8%	8.1%	0.90/10,000	
Central China	100.0%	100.0%	87.5%	87.5%	100.0%	100.0%	12.5%	87.5%	100.0%	12.5%	0.75/10,000	
Northwest	100.0%	100.0%	78.6%	85.7%	100.0%	100.0%	21.4%	85.7%	85.7%	25.0%	0.75/10,000	
North China	100.0%	100.0%	60.0%	80.0%	100.0%	100.0%	44.0%	88.0%	96.0%	12.5%	0.67/10,000	
Northeast	100.0%	100.0%	87.5%	87.5%	100.0%	100.0%	37.5%	75.0%	87.5%	12.5%	0.52/10,000	

Supplemental Table 3. is labeled as an online only supplement.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Page 1	Epidemiology of suspected life-threatening perioperative anaphylaxis: a cross-sectional multicentre study in China
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 1	This nationwide survey showed an incidence of 1 in 11,360 but varied significantly by region. The underlying reason for this unique pattern remains unknown and could be due to environmental or genetic influences and requires further investigation.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 2	Previous investigators reported similar geographic difference in the frequency of POA and questioned if characteristics of distinct populations could contribute to the variation in incidence. To confirm geographic variation as a descriptor of POA, investigators called for repeated cross-sectional epidemiological surveys in different countries.
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 2	These findings underlie the first

				purpose of our study, to describe the incidence of all-cause life-threatening suspected POA in China. Information about genome associated migration ancestry within China helped us accomplish our second aim: to identify a population with a concentration of suspected POA which overlapped with established genome-related ancestry.
Methods				
Study design	4	Present key elements of study design early in the paper	Page 2	The Strobe checklist for cross-sectional studies was followed for the conduct and writing of this study.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 2-3	See the organization and process for multicentre data collection and quality assurance of data and collection process part
Participants	6	(a) <i>Cohort study</i>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i>—Give the eligibility criteria, and the sources and methods of selection of participants (b) <i>Cohort study</i>—For matched studies, give matching criteria and number of exposed and unexposed	Page 2-3	See the organization and process for multicentre data collection part and definition of terms part

<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case				
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 2-3	See the organization and process for multicentre data collection, quality assurance of data and collection process and definition of terms part
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 3	See the definition of terms , data collection and statistical analysis part
Bias	9	Describe any efforts to address potential sources of bias	Page 2-3	See the organization and process for multicentre data collection and quality assurance of data and collection process part
Study size	10	Explain how the study size was arrived at		This is a cross-sectional study aimed to describe the incidence of life-threatening suspected perioperative anaphylaxis. Therefore, it is unnecessary to calculate the study size

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 3	Anaphylaxis was defined using published guidelines.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Page 3	See the statistical analysis part
		(b) Describe any methods used to examine subgroups and interactions	Page 3	See the statistical analysis part
		(c) Explain how missing data were addressed	Page 3	If any data was missing, we asked the primary investigator to collect data again.
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	Page 3	See the statistical analysis part
		(e) Describe any sensitivity analyses		It's indispensable to do any sensitivity analyses
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 3	During the study period 5,078,118 surgical procedures were performed with general or local anaesthesia with sedation at the 112 hospitals. A total of 551 life threatening cases of suspected POA 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 POA into the database (Figure 1).
		(b) Give reasons for non-participation at each stage	Page 3	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.
		(c) Consider use of a flow diagram	Page 4	Fig 1.Flow chart of cases reported, excluded, and included
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 5	Table 1 Patient characteristics
		(b) Indicate number of participants with missing data for each variable of interest		There was no missing data for each variable of interest
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		This is a cross-sectional study
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time		
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	Page 3-5	See the results part
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 3-4	See the patient Populations with anaphylactic reaction and incidence of suspected perioperative anaphylaxis in each region of China part
		(b) Report category boundaries when continuous variables were categorized	Page 5	Hypotension caused cardiovascular collapse with systolic blood pressures that were unrecordable in 19 of 407 patients (4.7%), and <50mmHg in 76 patients(18.7%). All 292 patients with tachycardia exhibited another symptom and the majority (n=276; 94.5%) had concomitant severe hypotension.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		No relevant variables needed to estimate absolute risk

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Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		Variables in the study didn't need to do any subgroups, interactions, or sensitivity analyses
Discussion				
Key results	18	Summarise key results with reference to study objectives	Page 5	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. Further, the difference in incidence was observed for all northern compared to southern regions and this strongly suggests a systematic difference that is population based.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 7	There were limitations that arise from our aim to measure all-cause POA 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.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 7-8	In summary, averaged reactions that met clinical diagnostic criteria for

				all cause anaphylaxis in this study occurred in 1 in 11,360 surgical cases in China and was similar to that calculated for all cause cases from the NAP6. We observed a significant demarcation by geographic location with a higher frequency in the south (1 in 6,050) compared to the northern (1 in 19,262) regions. The findings overlap with ancestral migration patterns. We suggest that a genomic study of the south compared to northern populations of China may help address contributing causes of geographic variation in incidence of all cause POA.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 7	We used the NAP6 as a measure of external validity because this study collected information about similar severity of all cause reactions.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 9	This study was funded by National Centre for Medical Service Administration, National Health and Family Planning Commission, China [Bureau of Medical Administration (2019)No.049].

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.