



Incidence of and risk factors for perioperative or periprocedural anaphylaxis in the United States from 2005 to 2014

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ABSTRACT

Background: The estimated worldwide incidence of perioperative or periprocedural anaphylaxis (PA) is between 1 in 1250 and 1 in 20,000 procedures.

Objective: To evaluate the incidence of PA in the United States and compare patient characteristics and underlying risk factors using a large national database.

Methods: Using deidentified data from the nationwide inpatient sample from 2005 to 2014, we identified cases of PA through the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes and conducted a retrospective analysis.

Results: Among 35,647,347 surgeries and procedures, there were 5458 (0.015%) PA cases identified. The incidence of PA was 15.3 cases per 100,000 procedures. When compared with controls, PA cases had an increased mortality (3.4% vs 1.4%; $P < .001$), median length of stay (5 vs 3 days; $P < .001$), and median hospital cost (\$45,155 vs \$24,734; $P < .001$). The age group between 18 and 34 years (odds ratio [OR], 1.34; 95% confidence interval [CI], 1.13–1.58; $P < .001$) and female sex (OR, 1.40; 95% CI, 1.31–1.49; $P < .001$) were associated with increased odds of PA. Transplant (OR, 3.35; 95% CI, 2.59–4.34; $P < .001$), hematologic (OR, 1.63; 95% CI, 1.30–2.05; $P < .001$), vascular (OR, 1.49; 95% CI, 1.30–1.67; $P < .001$), and cardiac (OR, 1.47; 95% CI, 1.30–1.67; $P < .001$) procedures were at increased risk for PA. Several comorbidities were associated with PA including chronic pulmonary disease (OR, 1.41; 95% CI, 1.31–1.51; $P < .001$).

Conclusion: The incidence of PA is 1 in 6531 procedures, with a mortality of 1 in 191,652 procedures. PA has worsening outcomes compared with controls. The risk factors of PA include age, sex, procedure type, and comorbidities.

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Introduction

Perioperative or periprocedural anaphylaxis (PA) is a severe, potentially life-threatening hypersensitivity reaction occurring during the perioperative or periprocedural period. The estimated worldwide incidence of PA is between 1 in 1250 and 1 in 20,000 procedures.¹ The primary risk factors for PA include female sex and history of a previous reaction during a procedure.² The mechanism of PA is either by an IgE-dependent or an IgE-independent pathway (direct mast cell degranulation by means of mast cell G protein-coupled receptor,³ IgG-dependent neutrophil platelet activation factor release,⁴ and complement activation⁵); however, PA remains a clinical diagnosis.⁶

The incidence of PA in the United States remains unknown because previous reports are limited to a few single-center retrospective studies.^{7–11} Nationwide and global data on risk factors of PA are lacking. The objectives of this study were to evaluate the incidence of PA in the United States and compare patient characteristics and underlying risk factors using a large national database.

Methods

Study Design and Data Source

We conducted a retrospective analysis of the data from the nationwide inpatient sample (NIS) from 2005 to 2014. The NIS is part of the Healthcare Cost and Utilization Project, which is the largest collection of longitudinal hospital care databases in the United States. This database includes all-payer discharge data from greater than 1200 hospitals to approximate a 20% stratified sample of US hospitals.¹² Public data from the NIS is deidentified, obviating the need for institutional review board approval and informed consent. This study adhered to the reporting guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology.¹³

Participants

We used the clinical classifications software (CCS) codes, which classifies the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* procedure codes into clinically meaningful categories to identify all procedures (eTable 1). We excluded the CCS codes (eTable 2) that would not be potentially associated with the development of anaphylaxis (eg, plain chest x-ray examination) or procedures that are known to be associated with drug hypersensitivity reactions (eg, hypersensitivity reactions secondary to chemotherapy) with a clear causative agent. Radiologic procedures, including computed tomography with contrast and magnetic resonance imaging studies, were not included. Organ-specific procedures that included radiocontrast media, which require conscious sedation, were included in the analyses (eg, left heart catheterization). We then categorized the CCS codes by organ system, anatomic localization, or surgical specialty (eTable 1). We used ICD-9-CM codes to identify cases of anaphylaxis during a procedure. We adapted previously validated criteria to identify cases of inpatient anaphylaxis.¹⁴ Criterion A identified patients who had ICD-9-CM codes 995.0 (other anaphylactic shock) or 999.4 (anaphylactic reaction to serum). Criterion B identified patients through the following ICD-9-CM codes of symptom combination: (1) 995.3 (allergy unspecified) or 995.2 (other unspecified adverse effect or drug) or E930-E949 (drugs, medicinal, and biological substance causing adverse effects in therapeutic use), (2) 458.9 (hypotension), and (3) either 519.11 (bronchospasm) or 786.1 (stridor). Controls were also identified from the database as all patients that underwent a procedure or surgery without PA during the same study period.

Variables

We analyzed PA cases by categorizing patients into 4 age groups (<18, 18–34, 35–64, ≥65 years old), sex, race (White and non-White), teaching hospital status (teaching and nonteaching), admission type (elective and nonelective), length of stay, total charges, mortality, and US region (Northeast, Midwest, South, and West). The US region categories represent standardized geographic divisions defined by the US Census Bureau. Procedures were categorized by organ system as follows: (1) cardiac; (2) vascular; (3) general surgery-gastrointestinal (GI); (4) musculoskeletal; (5) skin and breast; (6) obstetrics-gynecology (OB-GYN); (7) neurologic; (8) thoracic; (9) genitourinary-urologic; (10) hematologic; (11) transplant; (12) ears, nose, and throat (ENT); (13) ophthalmic; and (14) endocrine. Comorbidity measures included hypertension, fluid and electrolyte disorders,

chronic pulmonary disease, uncomplicated diabetes mellitus, iron deficiency anemia, obesity, renal failure, hypothyroidism, depression, peripheral vascular disorder, coagulopathy, congestive heart failure, neurologic disorder, weight loss, diabetes mellitus with complications, valvular disease, psychoses, rheumatoid arthritis-collagen vascular, alcohol abuse, drug abuse, pulmonary circulation disorders, liver and biliary disease, solid tumor without metastasis, metastatic cancer, chronic blood loss anemia, paralysis, and lymphoma. Data on teaching hospital status were not available in the NIS database from the years 2012 to 2014.

Statistical Analysis

The overall trends over time or between the groups for categorical variables were completed using χ^2 tests. Continuous variables were evaluated using the Kruskal-Wallis test. The potential risk factors for anaphylaxis were evaluated using logistic regression models. The odds ratios (OR) and 95% confidence intervals (CI) for those ORs were presented from those models. Trends over the years with respect to the rate of anaphylaxis were also evaluated using the logistic regression models. The analysis was completed using the Statistical Analysis System version 9.4 (SAS Institute, Cary, North Carolina).

Results

Population

Over the 10-year time frame of the study, 5458 (0.015%) surgeries and procedures were associated with PA from a total of 35,647,347 surgeries and procedures (Table 1). The median age of patients with PA was 57 years, 59% were women, 71% were White, 70% were nonelective procedures, and 54% were performed at teaching hospitals (Table 2). The greatest proportion of PA was among patients aged 35 to 64 years (46%) and occurred in the southern region of the United States (38%). The mortality of PA was 1 in 191,652 (0.00052%) surgeries and procedures.

Characteristics of Patients With PA Compared With Controls

When compared with controls, patients with PA were older (median age, 57 vs 51 years, respectively; $P < .001$), had longer hospital lengths of stay (median stay, 5 vs 3 days, respectively; $P < .001$), and had higher hospital costs (median, \$45,155 vs \$24,743, respectively; $P < .001$) (Table 2). Patients who experienced PA had increased incidence of mortality (3.4%; 95% CI, 2.9–3.9) compared with controls (1.4%; 95% CI, 1.4–1.4).

Time Trends of PA Cases

The proportion of PA cases in teaching hospitals increased from 2005 to 2011, with a peak in 2010 (P for trend $< .001$). Information on teaching hospital status was not available from the years 2012 to 2014 from the NIS database. There were no statistically significant changes over time from 2005 to 2014 in the proportion of PA cases based on sex, race, US region, admission type, or mortality (Table 1).

Rates of PA by Procedure Type

From 2005 to 2014, there were 15.3 (95% CI, 14.9–15.7) PA cases per 100,000 procedures with an increase of the overall cases per year from 10.9 per 100,000 procedures in 2005 to 20.7 per 100,000 procedures in 2014 (Table 3). Transplant procedures had the highest rate of PA (107.0; 95% CI, 85.8–131.8), whereas the lowest rate was in OB-GYN procedures (4.0; 95% CI, 3.6–4.4). The highest number of PA events overall occurred in cardiac procedures (1336 events), partially in keeping with the high number of cardiac procedures performed. Interestingly, though more procedures were performed in general surgery-GI and musculoskeletal categories, fewer PA cases occurred. Most rates of PA by procedure type have

Table 1

Overall Cases and Characteristics of Patients With Perioperative or Periprocedural Anaphylaxis Patients From 2005 to 2014

Characteristic ^a	Year											P value
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total	
Overall cases	411	420	459	568	571	597	648	556	569	659	5458	
Age, y												<.001
<18	8.0	5.7	7.0	3.7	3.7	6.9	3.9	4.0	6.9	5.9	5.4	
18–34	16.1	16.0	15.3	15.7	14.9	10.6	13.4	12.9	12.0	10.5	13.5	
35–64	39.9	50.0	49.0	49.1	46.4	46.9	46.0	44.8	45.3	45.5	46.3	
≥65	36.0	28.3	28.8	31.5	35.0	35.7	36.7	38.3	35.9	38.1	34.8	
Sex												.77
Female	61.6	60.7	59.9	58.6	59.5	59.5	60.3	56.8	58.9	56.1	59.1	
Male	38.4	39.3	40.1	41.4	40.5	40.5	39.7	43.2	41.1	43.9	40.9	
Race												.57
White	75.5	72.7	68.9	72.2	71.0	71.7	72.6	72.6	68.3	70.1	71.4	
Non-White	24.5	27.3	31.1	27.8	29.0	28.3	27.4	27.7	31.7	29.9	28.6	
US region												.20
Northwest	20.4	19.3	17.2	15.1	15.9	18.1	17.0	18.2	19.5	20.2	18.0	
Midwest	23.4	20.7	22.4	24.8	20.7	22.6	23.1	22.1	24.4	27.8	23.4	
South	36.3	38.1	37.7	37.7	43.1	37.4	39.5	38.8	38.0	34.4	38.1	
West	20.0	21.9	22.7	22.4	20.3	21.9	20.4	20.9	18.1	17.6	20.5	
Teaching hospital status												<.001
Non-teaching	54.5	49.8	42.3	44.5	45.2	39.9	46.0	—	—	—	45.6	
Teaching	45.5	50.2	57.7	55.5	54.8	60.1	54.0	—	—	—	54.4	
Admission type												.36
Nonelective	68.1	68.0	71.0	69.7	71.4	69.7	69.1	72.3	74.3	72.8	70.8	
Elective	31.9	32.0	29.0	30.3	28.6	30.3	30.9	27.7	25.7	27.2	29.2	
Mortality	2.4	4.0	3.1	3.5	2.5	4.7	3.1	2.7	4.4	3.5	3.4	.42

NOTE. The em dash indicates that data are not available.

^aValues are percentage of perioperative or periprocedural anaphylaxis unless otherwise specified.

increased over time, except for transplant, hematologic, endocrine, and OB-GYN procedures.

Risk Factors of PA

Patients aged 18 to 34 years had an increased risk for PA compared with patients younger than 18 years (OR, 1.34; 95% CI, 1.13–1.58; $P < .001$) (Table 4), whereas patients aged 65 years or older had a decreased risk of PA (OR, 0.71; 95% CI, 0.61–0.83; $P < .001$) relative to patients younger than 18 years of age. Women had an increased risk of PA compared with men (OR, 1.40; 95% CI, 1.31–1.49; $P < .001$). White patients had an increased risk for PA compared with non-White patients (OR, 1.08; 95% CI, 1.01–1.15; $P = .03$). There were no statistically significant differences in PA cases by admission type (Table 4). Teaching hospital status was not analyzed because there were insufficient numbers of cases for analysis.

Risk Factors of PA by Procedure Type and Comorbid Conditions

Cardiac, hematologic, transplant, and vascular procedures had an increased risk of PA, whereas endocrine, general surgery-GI, genitourinary-urology, musculoskeletal, neurologic, OB-GYN, and thoracic procedures had a decreased risk of PA compared with skin and breast procedures. There were no statistically significant differences in PA cases by ENT and ophthalmic procedures (Table 4). The top 5 concomitant disorders that increased the risk of PA included fluid and electrolyte disorders (OR, 1.93; 95% CI, 1.80–2.06; $P < .001$), malignancy comprising lymphoma (OR, 1.64; 95% CI, 1.26–2.06; $P < .001$) and nonmetastatic solid tumors (OR, 1.55; 95% CI, 1.30–1.85; $P < .001$), coagulopathy (OR, 1.60; 95% CI, 1.44–1.78; $P < .001$), and chronic pulmonary disease (OR, 1.41; 95% CI, 1.31–1.51; $P < .001$) (Table 4). Procedures with concomitant alcohol abuse (OR, 0.79; 95% CI, 0.63–0.99; $P = .04$) and liver and biliary disease (OR, 0.78; 95% CI, 0.65–0.93; $P = .007$) had a decreased risk of PA.

Discussion

This is the first nationwide study of PA in the United States. The United States does not currently have a specialized network (unlike

France, the United Kingdom, New Zealand, Australia, and Denmark) to study perioperative anaphylaxis. The primary focus in previous studies has been on sex, age, and causative substance in describing PA. Previous studies from individual institutions in the United States had a total of approximately 200 patients who had PA.^{7–11} This large retrospective analysis identified 5458 PA cases in the United States between 2005 and 2014 and enabled the evaluation of multiple variables. Primary findings previously unrealized include patients with PA who were older (a median of 6 years older than controls), had longer hospital stays (median of 2 more days), and higher inpatient cost (median, \$20,000 more than controls). Surprisingly, compared with patients younger than 18 years of age, patients aged 18 to 34 years had a higher risk of PA, and patients aged 65 years or older had a lower risk. As noted in previous studies from France,² Italy,¹⁵ Australia,¹⁶ Belgium,¹⁷ and the Republic of China,¹⁸ women were more likely to develop PA than men. Mortality in patients with PA was higher than controls (3.4% vs 1.4%).

Previous studies performed in the United States were not designed to evaluate incidence.^{7–11} Incidence has been found to vary between studies and countries given the variables such as underlying genetic differences and environmental exposures, differing anesthesia compounds and practices, and difficulty in clinical recognition and evaluation. We found that out of 100,000 procedures, 15.3 patients, or 1 in 6531, developed PA between 2005 and 2014. In contrast, a previous report from 3 combined French databases over an 8-year period estimated a rate of 100.6 (95% CI, 76.2–125.3) cases per million procedures or 1 in 10,000 between 1997 and 2004.² Given the differences in risk of PA depending on the type of procedure, the United States may have a different proportion of procedures resulting in a different incidence of PA. A possible explanation for our findings is that PA is more common than previously reported, and improved awareness, diagnostic methods, and coding might have generated more accurate data. PA poses a diagnostic challenge for health care providers, which results in PA underreporting.^{1,2} The Sixth National Audit Project (NAP6)¹⁹ from the United Kingdom, which only included life-threatening PA cases, found an incidence of 1 in 10,000 procedures; however, the true

Table 2

Characteristics of Perioperative or Periprocedural Anaphylaxis and Controls From 2005 to 2014

Characteristic	PA cases (n = 5458) (%)	Controls (n = 35,641,889) (%)	P value
Age, y			<.001
Median (IQR)	57 (41-69)	51 (29-69)	
Mean (SD)	54.1 (20.15)	48.1 (24.79)	
Groups			<.001
<18	297 (5.4)	3,600,883 (10.1)	
18-34	736 (13.5)	8,463,166 (23.7)	
35-64	2528 (46.3)	12,483,314 (35)	
≥65	1897 (34.8)	11,094,526 (31.1)	
Sex			.31
Female	3223 (59.1)	21,287,339 (59.7)	
Male	2235 (40.9)	14,354,550 (40.3)	
Race			<.001
White	3336 (71.4)	20,326,029 (68)	
Black	556 (11.9)	3,819,114 (12.8)	
Hispanic	450 (9.6)	3,693,267 (12.4)	
Asian or Pacific Islander	148 (3.2)	825,560 (2.8)	
Native American	25 (0.5)	195,000 (0.7)	
Other	158 (3.4)	1,036,495 (3.5)	
Unknown	785	5,744,722	
Region			.40
Northeast	984 (18)	6,388,548 (17.9)	
Midwest	1275 (23.4)	8,217,254 (23.1)	
South	2080 (38.1)	13,959,829 (39.2)	
West	1119 (20.5)	7,076,258 (19.9)	
Teaching hospital status			<.001
Nonteaching	1659 (45.6)	12,997,396 (50.4)	
Teaching	1980 (54.4)	12,814,981 (49.6)	
Missing	1819	9,829,512	
Admission type			<.001
Nonelective	3853 (70.8)	21,779,108 (61.3)	
Elective	1590 (29.2)	13,747,292 (38.7)	
Missing	15	114,715	
Length of stay			<.001
Mean (SD)	7.9 (9.98)	4.8 (6.98)	
Median (range)	5 (0.0-134.0)	3 (0.0-365.0)	
Total charges			<.001
Mean (SD)	83,660.7 (124,809.22)	43,005.8 (69,767.74)	
Median (Range)	45,155 (38.0-1,899,245.0)	24,734 (25.0-499,997.0)	
Mortality	186 (3.4; 95% CI, 2.9-3.9)	498,898 (1.4; 95% CI, 1.4-1.4)	<.001

Abbreviations: CI, confidence interval; IQR, interquartile range; PA, perioperative or periprocedural anaphylaxis.

incidence might have been 70% higher²⁰ (or 1 in 7000) because of unconfirmed incomplete patient data, which is similar to our findings (1 in 6531). Finally, the incidence in our cohort may be higher than in the French study because we included all cases regardless of the mechanism (IgE-mediated or non-IgE-mediated), whereas the French study included only IgE-mediated cases confirmed by the

evidence of a positive immediate hypersensitivity to the drug through skin or in vitro testing.² The percentage of IgE-mediated vs non-IgE-mediated causes of PA varies by center and study, with non-IgE-mediated cases being approximately 40% in many studies.¹

To date, there is little consensus on how age, sex, and type of procedure affect the risk of a patient developing PA. Our data

Table 3

Rates of Perioperative or Periprocedural Anaphylaxis by Procedure Type Per 100,000 Procedures From 2005 to 2014

Category ^a	Actual PA cases	Total number of procedures	Year										P value	Overall rate per 100,000 procedures (95% CI)
			2005	2006	2007	2008	2009	2010	2011	2012	2013	2014		
Overall cases	5458	35,647,347	10.9	11.0	12.1	14.9	15.8	16.7	17.7	17.1	17.8	20.7	<.001	15.3 (14.9-15.7)
Transplant	88	82,243	93.8	79.4	135.1	116.8	105.5	153.2	126.8	25.4	90.6	126.3	.85	107.0 (85.8-131.8)
Vascular	1047	2,370,689	28.2	28.8	34.9	41.0	51.3	50.1	44.9	48.2	53.7	60.3	<.001	44.2 (41.5-46.9)
Hematologic	110	251,680	12.6	44.4	58.8	24.2	59.1	25.5	31.8	46.0	60.9	51.7	.09	43.7 (35.9-52.7)
Cardiac	1336	4,288,838	21.3	22.2	25.7	31.1	28.8	32.9	36.9	41.8	37.2	44.3	<.001	31.2 (29.5-32.9)
Ophthalmic	13	50,269	16.0	0	0	0	20.6	55.7	40.7	43.5	69.8	24.7	.03	25.9 (13.8-44.2)
Skin and breast	373	1,473,056	19.1	24.0	19.1	25.5	27.8	26.6	25.9	21.8	35.5	30.9	.009	25.3 (22.8-28.0)
ENT	73	288,522	17.7	6.7	10.3	20.4	41.6	23.9	27.0	37.5	18.2	56.3	.001	25.3 (19.8-31.8)
Thoracic	230	1,108,560	10.9	15.6	21.7	19.3	17.1	23.1	20.4	29.8	20.2	30.1	.001	20.7 (18.2-23.6)
Neurologic	233	1,449,768	12.0	9.0	15.9	16.8	15.5	16.5	19.0	15.6	14.1	28.9	.002	16.1 (14.1-18.3)
General surgery-GI	892	6,449,876	12.8	9.2	11.4	13.2	13.2	15.8	18.6	12.0	14.5	17.9	<.001	13.8 (12.9-14.8)
Musculoskeletal	541	5,532,370	5.5	7.5	5.7	9.0	10.0	12.0	11.6	11.4	10.8	13.3	<.001	9.8 (9.0-10.6)
Endocrine	12	175,185	5.2	5.2	15.7	4.6	11.2	0	4.9	6.9	15.7	0	.84	6.8 (3.5-12.0)
GU-urologic	154	3,248,799	3.0	3.0	2.7	7.1	4.1	4.8	5.9	4.5	6.8	6.5	.004	4.7 (4.0-5.6)
OB-GYN	356	8,877,492	3.8	3.5	3.5	3.8	4.5	2.9	4.9	4.5	4.9	4.2	.11	4.0 (3.6-4.4)

Abbreviations: ENT, ears, nose, and throat; GI, gastrointestinal; GU, genitourinary; OB-GYN, obstetrics-gynecology; PA, perioperative or periprocedural anaphylaxis.

^aValues are rate per 100,000 procedures.

Table 4
Multivariable Predictors of Perioperative or Periprocedural Anaphylaxis

Characteristic	OR (95% CI)	P value
Age, y		
<18	Reference	
18–34	1.34 (1.13–1.58)	<.001
35–64	1.15 (0.99–1.33)	.07
≥65	0.71 (0.61–0.83)	<.001
Sex		
Female	1.40 (1.31–1.49)	<.001
Male	Reference	
Race		
White	1.08 (1.01–1.15)	.03
Non-White	Reference	
Teaching hospital status		
Teaching	—	
Nonteaching	—	
Admission type		
Elective	0.92 (0.86–0.98)	.08
Nonelective	Reference	
Procedure type		
OB–GYN	0.14 (0.12–0.17)	<.001
GU–urology	0.27 (0.22–0.33)	<.001
Endocrine	0.31 (0.17–0.57)	<.001
Musculoskeletal	0.44 (0.38–0.51)	<.001
General surgery–gastrointestinal	0.51 (0.44–0.58)	<.001
Neurologic	0.64 (0.53–0.76)	<.001
Thoracic	0.74 (0.62–0.88)	<.001
ENT	1.11 (0.84–1.46)	.46
Ophthalmic	1.41 (0.81–2.46)	.28
Cardiac	1.47 (1.30–1.67)	<.001
Vascular	1.49 (1.30–1.67)	<.001
Hematology	1.63 (1.30–2.05)	<.001
Transplant	3.35 (2.59–4.34)	<.001
Skin and breast	Reference	
Comorbidity measures		
Liver and biliary disease	0.78 (0.65–0.93)	.007
Alcohol abuse	0.82 (0.69–0.97)	.02
Diabetes mellitus, uncomplicated	0.91 (0.80–1.05)	.21
Weight loss	0.92 (0.81–1.05)	.23
Hypertension	0.95 (0.89–1.02)	.16
Deficiency anemia	0.97 (0.90–1.05)	.45
Diabetes mellitus with complications	0.98 (0.91–1.06)	.59
Hypothyroidism	1.01 (0.91–1.11)	.87
Renal failure	1.01 (0.91–1.11)	.88
Paralysis	1.04 (0.87–1.26)	.66
Congestive heart failure	1.04 (0.92–1.17)	.49
Drug abuse	1.05 (0.89–1.25)	.55
Depression	1.05 (0.96–1.16)	.30
Psychoses	1.12 (0.96–1.30)	.15
Metastatic cancer	1.16 (0.97–1.39)	.11
Chronic blood loss anemia	1.18 (0.98–1.41)	.08
Rheumatoid arthritis–collagen vascular disease	1.22 (1.04–1.43)	.01
Neurologic disorder	1.23 (1.10–1.38)	<.001
Peripheral vascular disorder	1.23 (1.11–1.37)	<.001
Obesity	1.24 (1.13–1.35)	<.001
Acquired immunodeficiency syndrome	1.26 (0.76–2.10)	.37
Pulmonary circulation disorders	1.30 (1.09–1.55)	.004
Valvular disease	1.40 (1.20–1.61)	<.001
Chronic pulmonary disease	1.41 (1.31–1.51)	<.001
Solid tumor without metastasis	1.55 (1.30–1.85)	<.001
Coagulopathy	1.60 (1.44–1.78)	<.001
Lymphoma	1.64 (1.26–2.06)	<.001
Fluid and Electrolyte disorders	1.93 (1.80–2.06)	<.001

NOTE. The em dash indicates that data were not available. Abbreviations: ENT, ears, nose, and throat; GI, gastrointestinal; GU, genitourinary; OB–GYN, obstetrics–gynecology; OR, odds ratio.

regarding how these factors impact the risk for PA is comparable with previous studies. In our cohort, the greatest proportion of PA cases occurred in patients between 35 and 64 years of age, which is consistent with a previous French study.² Previous studies did not analyze age as a risk factor for PA. We found that patients between 18 and 34 years of age had a higher risk of PA, whereas patients aged 65 years or older had a lower risk of PA. This finding may be explained by the decreasing acquired immune function through

progressive loss of follicular T-helper cell–dependent class-switched antibody response, which occurs with aging.²¹

The proportion of pediatric cases (5.4%) in our cohort was half of what was previously reported by Mertes et al.² In a previous subgroup analysis of a large French study² of 2516 patients from 1997 through 2004, 10.6% were pediatric cases, with natural rubber latex as the main identifiable cause of PA. The lower proportion of cases in our cohort may reflect the decreased use of natural rubber latex products in recent years by health care providers.²² Furthermore, a more recent multicenter pediatric retrospective review of 29 cases confirmed that only 1 case (3%) was secondary to natural rubber latex.²³ A European report of severe critical anesthetic events in a pediatric cohort found a single case of latex-induced PA²⁴ and no cases were reported in the NAP6.²⁵ Our findings are similar to those from a large Belgian study that analyzed 715 patients from 2001 to 2018 who were referred for allergy evaluation because of suspected PA. In that study, 6.6% of the cases of PA were pediatric patients; and neuromuscular blocking agents (NMBA) and antibiotics accounted for most of the cases.²⁶

Consistent with the findings reported by other PA studies,^{2,7–11,15–18,26} we found a greater proportion of women relative to men with PA. PA follows a similar pattern of sex-dependent changes as asthma.² In our cohort, women were 40% more likely to develop PA compared with men. Sex-specific differences in the adaptive immune responses may explain this finding. B cell numbers and antibody production are increased in women compared with men.²⁷ These differences are probably driven by sex hormones and genetic factors. Another possible explanation is a higher sensitization in women on the use of cosmetics, which share similar chemical structures with NMBAs,²⁸ which is a frequently implicated cause of PA.

Compared with age and sex, data showing the type of procedure as a risk factor of PA are more limited. In our cohort, transplant procedures presented the highest rate of PA (1 in 935) and OB–GYN procedures had the lowest incidence of PA (1 in 25,000) and the lowest risk for PA (OR, 0.14; 95% CI, 0.12–0.17; $P < .001$). In contrast, Huang et al¹⁸ evaluated the risk of PA depending on the surgical approach in patients who underwent surgeries between 2012 and 2017, excluding transplants and OB–GYN procedures, and they found that patients who underwent vascular or orthopedic approaches had the highest risk of experiencing PA.¹⁸ A possible explanation for our findings is the type of anesthesia used during a procedure. More complex procedures may require general anesthesia (eg, transplant) vs simpler procedures that may require regional (eg, cesarean section) or monitored anesthesia (eg, esophagogastroduodenoscopy). The type of anesthesia (general anesthesia, regional, or monitored anesthesia care) used during a procedure seems to affect the likelihood of PA. In a retrospective report of PA cases from a single large US tertiary care referral center, most cases (9 of 10) underwent general anesthesia, whereas the minority had either regional or monitored anesthesia care.⁷ Other studies performed in the United States did not report the anesthesia type used during PA.^{8–11} Furthermore, the incidence of NMBA-induced PA (1 in 5434) was almost double than that of all-cause PA (1 in 10,000) in a large French study.² However, a contemporary report suggested that differences in anesthesia types (local/regional vs general) might not be marked in their effect over PA risk.¹⁸ Further studies with large samples are warranted to more accurately define the influence of anesthesia type over the risk of developing PA. Another explanation is the medications and substances concomitantly used before or during the procedure. Cardiovascular procedures could potentially include beta blockers and angiotensin-converting enzyme inhibitors, which have been previously associated with an increased risk for worsening PA outcomes.²⁵ A more recent study did not find a statistically substantial effect of these medications on the risk of developing PA.¹⁸ Even

though vascular procedures—which frequently require contrast media (eg, embolectomies) and the use of beta blockers with hyperosmolar contrast media—have been previously associated with increased risk for anaphylaxis,²⁹ a large contemporary study revealed that there is no association between the use of beta blockers and increased risk of contrast media–induced anaphylaxis when low osmolar contrast media is used.³⁰ The type of contrast media used during vascular procedures was not reported by Huang et al.¹⁸

We found a higher rate of PA in nonelective procedures than in controls. However, this finding was not statistically significant in multivariate analysis ($P = .08$). A French study reported that procedures performed in an emergency setting were associated with an increased risk for NMBA-induced fatal PA in multivariate analysis (OR, 2.5).³¹ The authors concluded that this might be because of the use of succinylcholine, which is one of the most common NMBAs causing PA during emergent intubation.³¹ Further epidemiologic studies are needed to confirm the nonelective procedure as a risk factor for all-cause PA.

Other risk factors (such as previous allergic reactions during anesthesia, known drug or food allergies, history of surgeries with exposure to latex) have been reported to affect the risk of developing PA.² However, the influence of comorbidities on the risk of PA has not been studied. Fluid and electrolyte disorders, malignancy (including lymphoma and nonmetastatic solid tumor), coagulopathy, and chronic pulmonary disease were the top 5 comorbidities that increased the risk of PA. In our cohort, asthma was included within the chronic pulmonary disease, and we were unable to further subdivide this category; however, asthma has not been reported to be a risk factor for PA.² We also did not find a significant change in the risk of PA in patients with hypertension (OR 0.95; 95% CI, 0.89–1.02; $P = .16$), which is similar to what was reported by Huang et al.¹⁸ It is unclear as to what definition of alcohol abuse and severity of the liver disease was used in the NIS database; however, our data revealed that these comorbidities had a decreased risk of PA. It is possible that these findings are because of the fibrotic state of the liver in advanced liver disease, which could cause the recruitment of mast cells to the liver leading to a more localized and contained degranulation of these effector cells compared with patients without these comorbidities.³² Another explanation is the relative immunosuppressive effect of alcohol abuse on the bone marrow.³³ Finally, PA may be underrecognized in patients with liver disease because of hypotension attributed to third spacing rather than anaphylaxis.

There are some important limitations that need consideration, all of which are inherent to this type of study. As with most observational studies, elimination of unmeasured cofounders is sometimes not feasible, and the use of large databases such as the NIS means that data may not be standardized, especially regarding coding and individual diagnoses. We were unable to identify the causative agents or clinical characteristics of PA because this information is not captured by this database. Finally, it is difficult to separate index cases of PA from repeat episodes of PA in the same patient with studies of this nature. However, given the characteristics of this large cohort, our study's data are generalizable to similar populations in the United States.

To the best of our knowledge, this is the first US nationwide study on perioperative anaphylaxis to be reported. The incidence of PA is 1 in 6531 procedures, with a mortality of 1 in 191,652 procedures. Individuals with PA have higher mortality rates, length of stay, and inpatient costs than those of controls. The risk factors for PA include age (18–34 years), female sex, procedure type (transplant, hematologic, vascular, and cardiac procedures), and comorbid conditions. Further comprehensive nationwide studies within collaborating academic centers with harmonized immediate drug

allergy skin testing protocols used for perioperative hypersensitivity evaluation are needed to increase our understanding of the epidemiologic trends, risk factors, etiologic agents, and outcomes to help guide recommendations on future procedures after a diagnosis of PA.

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Supplementary Data

eTable 1

Clinical Classifications Software Procedure Code Category

Category	CCS code	Procedure
Neurologic	1	Incision and excision of CNS
	2	Insertion, replacement, or removal of extracranial ventricular shunt
	3	Laminectomy or excision intervertebral disk
	4	Diagnostic spinal tap
	5	Insertion of a catheter or spinal stimulator and injection into the spinal canal
	6	Decompression peripheral nerve
	7	Other diagnostic nervous system procedures
	8	Other nonoperating room or closed therapeutic nervous system procedures
	9	Other operating room therapeutic nervous system procedures
Endocrine	10	Thyroidectomy, partial or complete
	11	Diagnostic endocrine procedures
	12	Other therapeutic endocrine procedures
Transplant	13	Corneal transplant
	64	Bone marrow transplant
	105	Kidney transplant
Ophthalmic	176	Organ transplantation (other than bone marrow, corneal, or kidney)
	14	Glaucoma procedures
	15	Lens and cataract procedures
	16	Repair of a retinal tear, detachment
	17	Destruction of lesion of retina and choroid
	18	Diagnostic procedures on the eye
	19	Other therapeutic procedures on eyelids, conjunctiva, or cornea
	20	Other intraocular therapeutic procedures
	21	Other extraocular muscle and orbit therapeutic procedures
ENT	22	Tympanoplasty
	23	Myringotomy
	24	Mastoidectomy
	25	Diagnostic procedures on the ear
	26	Other therapeutic ear procedures
	27	Control of epistaxis
	28	Plastic procedures on the nose
	29	Dental procedures
	30	Tonsillectomy and/or adenoidectomy
	31	Diagnostic procedures on the nose, mouth, and pharynx
	32	Other nonoperating room therapeutic procedures on the nose, mouth, and pharynx
	33	Other operating room therapeutic procedures on the nose, mouth, and pharynx
	35	Tracheoscopy and laryngoscopy with biopsy
	36	Lobectomy or pneumonectomy
	37	Diagnostic bronchoscopy and biopsy of bronchus
Thoracic	38	Other diagnostic procedures on lung and bronchus
	39	Incision of pleura; thoracentesis; chest drainage
	40	Other diagnostic procedures of respiratory tract and mediastinum
	41	Other nonoperating room therapeutic procedures on the respiratory system
	42	Other operating room Rx procedures on respiratory system and mediastinum
	43	Heart valve procedures
	44	Coronary artery bypass graft
	45	Percutaneous transluminal coronary angioplasty
	46	Coronary thrombolysis
Cardiac	47	Diagnostic cardiac catheterization; coronary arteriography
	48	Insertion, revision, replacement, or removal of a cardiac pacemaker or cardioverter/defibrillator
	49	Other operating room heart procedures
	50	Extracorporeal circulation auxiliary to open-heart procedures
	51	Endarterectomy of the vessel of head and neck
	52	Aortic resection, replacement or anastomosis

(continued on next page)

eTable 1 (continued)

Category	CCS code	Procedure
Vascular	53	Varicose vein stripping; lower limb
	54	Other vascular catheterization; not heart
	55	Peripheral vascular bypass
	56	Other vascular bypass and shunt (not heart)
	57	Creation, revision, and removal of arteriovenous fistula or vessel-to-vessel cannula for dialysis
	59	Other operating room procedures on vessels of head and neck
	60	Embolectomy and endarterectomy of lower limbs
	61	Other operating room procedures on vessels other than head and neck
	62	Other diagnostic cardiovascular procedures
	63	Other nonoperating room therapeutic cardiovascular procedures
Hematology	65	Bone marrow biopsy
	66	Procedures on spleen
	67	Other therapeutic procedures, hemic and lymphatic system
General surgery/GI	68	Injection or ligation of esophageal varices
	69	Esophageal dilatation
	70	Upper gastrointestinal endoscopy, biopsy
	71	Gastrostomy, temporary and permanent
	72	Colostomy, temporary and permanent
	73	Ileostomy and other enterostomies
	74	Gastrectomy, partial and total
	75	Small bowel resection
	76	Colonoscopy and biopsy
	77	Proctoscopy and anorectal biopsy
	78	Colorectal resection
	79	Local excision of a large intestine lesion (not endoscopic)
	80	Appendectomy
	81	Hemorrhoid procedures
	82	Fluoroscopy of the biliary and pancreatic ducts (ERCP, ERC, and ERP)
	83	Biopsy of liver
	84	Cholecystectomy and common duct exploration
	85	Inguinal and femoral hernia repair
	86	Other hernia repairs
	87	Laparoscopy (GI only)
	88	Abdominal paracentesis
	89	Exploratory laparotomy
	90	Excision, lysis of peritoneal adhesions
	92	Other bowel diagnostic procedures
	93	Other nonoperating room upper GI therapeutic procedures
	94	Other operating room upper GI therapeutic procedures
	95	Other nonoperating room lower GI therapeutic procedures
	96	Other operating room lower GI therapeutic procedures
	97	Other gastrointestinal diagnostic procedures
	98	Other nonoperating room gastrointestinal therapeutic procedures
	99	Other operating room gastrointestinal therapeutic procedures
GU/urology	100	Endoscopy and endoscopic biopsy of the urinary tract
	101	Transurethral excision, drainage, or removal of urinary obstruction
	102	Ureteral catheterization
	103	Nephrotomy and nephrostomy
	104	Nephrectomy, partial or complete
	106	Genitourinary incontinence procedures
	107	Extracorporeal lithotripsy, urinary
	109	Procedures on the urethra
	110	Other diagnostic procedures of the urinary tract
	111	Other nonoperating room therapeutic procedures of urinary tract
	112	Other operating room therapeutic procedures of urinary tract
	113	Transurethral resection of the prostate
	114	Open prostatectomy
	115	Circumcision
	116	Diagnostic procedures, male genital

(continued on next page)

eTable 1 (continued)

Category	CCS code	Procedure
OB/GYN	117	Other nonoperating room therapeutic procedures, male genital
	118	Other operating room therapeutic procedures, male genital
	119	Oophorectomy, unilateral and bilateral
	120	Other operations on the ovary
	121	Ligation or occlusion of fallopian tubes
	122	Removal of ectopic pregnancy
	123	Other operations on fallopian tubes
	124	Hysterectomy, abdominal and vaginal
	125	Other excision of the cervix and uterus
	126	Abortion (termination of pregnancy)
	127	D&C; aspiration after delivery or abortion
	128	Diagnostic D&C
	129	Repair of cystocele and rectocele; obliteration of vaginal vault
	130	Other diagnostic procedures, female organs
	131	Other nonoperating room therapeutic procedures, female organs
	132	Other operating room therapeutic procedures, female organs
	133	Episiotomy
	134	Cesarean section
	137	Other procedures to assist delivery
Musculoskeletal	138	Diagnostic amniocentesis
	140	Repair of current obstetrical laceration
	141	Other therapeutic obstetrical procedures
	142	Partial excision bone
	143	Bunionectomy or repair of toe deformities
	144	Treatment, facial fracture or dislocation
	145	Treatment, fracture or dislocation of radius and ulna
	146	Treatment, fracture or dislocation of hip and femur
	147	Treatment, fracture or dislocation of the lower extremity (other than hip or femur)
	148	Other fracture and dislocation procedure
	149	Arthroscopy
	150	Division of joint capsule; ligament or cartilage
	151	Excision of semilunar cartilage of the knee
	152	Arthroplasty knee
	153	Hip replacement, total and partial
	154	Arthroplasty other than hip or knee
	155	Arthrocentesis
	156	Injections and aspirations of muscles; tendons; bursa; joints and soft tissue
	157	Amputation of lower extremity
Skin and breast	158	Spinal fusion
	159	Other diagnostic procedures on the musculoskeletal system
	160	Other therapeutic procedures on muscles and tendons
	161	Other operating room therapeutic procedures on bone
	162	Other operating room therapeutic procedures on joints
	163	Other nonoperating room therapeutic procedures on the musculoskeletal system
	164	Other operating room therapeutic procedures on the musculoskeletal system
	165	Breast biopsy and other diagnostic procedures on breast
	166	Lumpectomy, quadrantectomy of breast
	167	Mastectomy
	168	Incision and drainage, skin and subcutaneous tissue
	169	Debridement of a wound, infection, or burn
	170	Excision of skin lesion
	171	Suture of skin and subcutaneous tissue
	172	Skin graft
	173	Other diagnostic procedures on the skin and subcutaneous tissue
	174	Other nonoperating room therapeutic procedures on skin and breast
	175	Other operating room therapeutic procedures on skin and breast

Abbreviations: CCS, clinical classifications software; CNS, central nervous system; D&C, dilatation, and curettage; ENT, ears, nose, and throat; ERC, endoscopic retrograde cholangiography; ERCP, endoscopic retrograde cholangiopancreatography; ERP, endoscopic retrograde pancreatography; GI, gastrointestinal; GU, genitourinary; OB/GYN, obstetrics/gynecology.

eTable 2

Excluded Clinical Classifications Software Procedure Codes

CCS code	Procedure
34	Tracheostomy, temporary and permanent
58	Hemodialysis
91	Peritoneal dialysis
108	Indwelling catheter
135	Forceps, vacuum, and breech delivery
136	Artificial rupture of membranes to assist delivery
139	Fetal monitoring
177	Axial CT scan head
178	CT scan chest
179	CT scan abdomen
180	Other CT scan
181	Myelogram
182	Mammography
183	Routine chest x-ray examination
184	Intraoperative cholangiogram
185	Upper gastrointestinal x-ray examination
186	Lower gastrointestinal x-ray examination
187	Intravenous pyelogram
188	Cerebral arteriogram
189	Contrast aortogram
190	Contrast arteriogram of femoral and lower extremity arteries
191	Arterio- or venogram (not the heart and head)
192	Diagnostic ultrasound of head and neck
193	Diagnostic ultrasound of the heart (echocardiogram)
194	Diagnostic ultrasound of gastrointestinal tract
195	Diagnostic ultrasound of urinary tract
196	Diagnostic ultrasound of abdomen or retroperitoneum
197	Other diagnostic ultrasound
198	Magnetic resonance imaging
199	Electroencephalogram
200	Nonoperative urinary system measurements
201	Cardiac stress tests
202	Electrocardiogram
203	Electrographic cardiac monitoring
204	Swan-Ganz catheterization for monitoring
205	Arterial blood gases
206	Microscopic examination (bacterial smear; culture; toxicology)
207	Nuclear medicine imaging of bone
208	Nuclear medicine imaging of pulmonary
209	Nonimaging nuclear medicine probe or assay
210	Other nuclear medicine imaging
211	Radiation therapy
212	Diagnostic physical therapy
213	Physical therapy exercises, manipulation, and other procedures
214	Traction, splints, and other wound care
215	Other physical therapy and rehabilitation
216	Respiratory intubation and mechanical ventilation
217	Other respiratory therapy
218	Psychological and psychiatric evaluation and therapy
219	Alcohol and drug rehabilitation/detoxification
220	Ophthalmologic and otologic diagnosis and treatment
221	Nasogastric tube
222	Blood transfusion
223	Enteral and parenteral nutrition
224	Cancer chemotherapy
225	Conversion of cardiac rhythm
226	Other diagnostic radiology and related techniques
227	Other diagnostic procedures
228	Prophylactic vaccinations and inoculations
229	Nonoperative removal of foreign body
230	Extracorporeal shock wave other than urinary
231	Other therapeutic procedures

Abbreviations: CCS, clinical classifications software; CT, computed tomography.