Characterizing the Epidemiology of Perioperative Transfusion-associated Circulatory Overload

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ABSTRACT

Background: Transfusion-associated circulatory overload (TACO) is a leading cause of transfusion-related fatalities, but its incidence and associated patient and transfusion characteristics are poorly understood. To inform surgical transfusion practice and to begin mitigating perioperative TACO, the authors aimed to define its epidemiology.

Methods: In this retrospective cohort study, the medical records of adult patients undergoing noncardiac surgery with general anesthesia during 2004 or 2011 and receiving intraoperative transfusions were screened using an electronic algorithm for identification of TACO. Those patients who were screened as high probability for TACO underwent rigorous manual review. Univariate and multivariate analyses evaluated associations between patient and transfusion characteristics with TACO rates in a before-and-after study design.

Results: A total of 2,162 and 1,908 patients met study criteria for 2004 and 2011, respectively. The incidence of TACO was 5.5% (119 of 2,162) in 2004 *versus* 3.0% (57 of 1,908) in 2011 ($P < 0.001$), with comparable rates for men (4.8% [98 of 2,023]) and women (3.8% [78 of 2,047]) ($P = 0.09$). Overall, vascular (12.1% [60 of 497]), transplant (8.8% [17 of 193]), and thoracic surgeries (7.2% [10 of 138]) carried the highest TACO rates. Obstetric and gynecologic patients had the lowest rate (1.4% [4 of 295]). The incidence of TACO increased with volume transfused, advancing age, and total intraoperative fluid balance (all $P < 0.001$).

Conclusions: The incidence of perioperative TACO is similar to previous estimates in nonsurgical populations. There was a reduction in TACO rate between 2004 and 2011, with incidence patterns remaining comparable in subgroup analyses. Future efforts exploring risk factors for TACO may guide preventive or therapeutic interventions, helping to further mitigate this transfusion complication. **(Anesthesiology 2015; 122:21-8)**

SINCE the 1940s, circulatory overload after blood product transfusion has been reported in the medical literature.[1] Despite this recognition, transfusion-associated circulatory overload (TACO) was neither defined nor investigated as a separate entity until the 1990s.[2] With the initiation of passive reporting to the U.S. Food and Drug Administration in 2005, TACO has become increasingly recognized, and recent estimates suggest incidence rates as high as 11%.[3–5] During this time, TACO has accounted for 2 to 27% of the transfusion-related fatalities reported to the U.S. Food and Drug Administration, making it the second leading cause of transfusion-related death after transfusion-related acute lung injury (TRALI).*

Notably, most investigators evaluating the epidemiology of TACO have concentrated on patients in the intensive care unit (ICU).[3,5,6] As a result, the epidemiology of TACO and its resultant burden in surgical populations remains incompletely defined. Moreover, TACO is frequently overlooked in clinical practice and is infrequently reported to the transfusion medicine service.[7,8] Thus, the actual incidence of perioperative TACO remains poorly defined and is likely much greater than that currently reported in other patient

What We Already Know about This Topic

- Transfusion-associated circulatory overload is a leading cause of transfusion-related fatalities; however, its epidemiology after noncardiac surgery is not well characterized

What This Article Tells Us That Is New

- This retrospective cohort study evaluated 2,162 and 1,908 patients who received intraoperative transfusions during noncardiac surgery in 2004 and 2011, respectively
- A total of 119 patients (5.5%) in 2004 and 57 patients (3%) in 2011 met criteria for transfusion-associated circulatory overload
- The incidence of transfusion-associated circulatory overload increased with the volume of blood product transfused, advanced age, and total intraoperative fluid balance

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populations. Not only does this failure to appreciate TACO events contribute to our incomplete understanding of TACO epidemiology, but it may also result in suboptimal care delivery and unfavorable outcomes for patients.

Current data demonstrate that approximately 50% of all blood product transfusions take place in the perioperative setting.[9] Perioperative care providers are thus in an ideal position to recognize transfusion risks, which may allow for more appropriate transfusion therapies and for more timely and appropriate interventions in patients with transfusion-related complications such as TACO. Thus, it is imperative to more clearly define the epidemiology of perioperative TACO. To this end, we sought to define the incidence of TACO in a large cohort of patients who had undergone noncardiac surgery. In addition, we aimed to further describe the incidence of TACO as it relates to specific characteristics of patients and transfusion situations. Finally, in light of a recent report postulating that universal leukoreduction reduces the rate of TACO,[7] we assessed the impact of this intervention by evaluating the incidence of TACO in all patients who received transfusions before (2004) and several years after (2011) its implementation in 2005.

Materials and Methods

Study Design

In this retrospective cohort study evaluating the incidence of TACO, we analyzed the data abstracted from the electronic medical records (EMRs) of adult noncardiac surgery patients treated with general anesthesia at Mayo Clinic who had received intraoperative blood product transfusions in 2004 or 2011. All patients had previously given signed consent for the use of their medical records for research purposes, and the Mayo Clinic Institutional Review Board approved the study before its onset. The Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in the conduct of this study and in the reporting of its results.[10]

Study Population

Adult patients (aged ≥18 yr) who had undergone noncardiac surgical procedures with general anesthesia at our institution (Mayo Clinic, Rochester, Minnesota) during the calendar years 2004 or 2011 were identified from an institutional database (the perioperative data mart).[9] This database contains a near real-time duplicate of all patient data from monitored care environments. Data are stored and accessed *via* an open-access connectivity database using JMP statistical software (SAS Institute Inc., Cary, NC). The accuracy of this database has been previously described and validated.[9,11–13]

All adult noncardiac surgical patients who received intraoperative blood product transfusions were eligible for inclusion. Exclusion criteria included (1) denial of research authorization, (2) age younger than 18 yr, (3) previous inclusion in the study (*i.e.*, patients who had multiple eligible surgeries were included only once), (4) evidence of preoperative respiratory failure, (5) preoperative diffuse bilateral infiltrates evident on chest radiographs, (6) death intraoperatively, (7) receipt of extracorporeal membrane oxygenation commenced intraoperatively before blood product transfusion, and (8) receipt of nongeneral anesthesia instead of general anesthesia (fig. 1). Notably, all subjects in the current study were specifically identified for inclusion in this

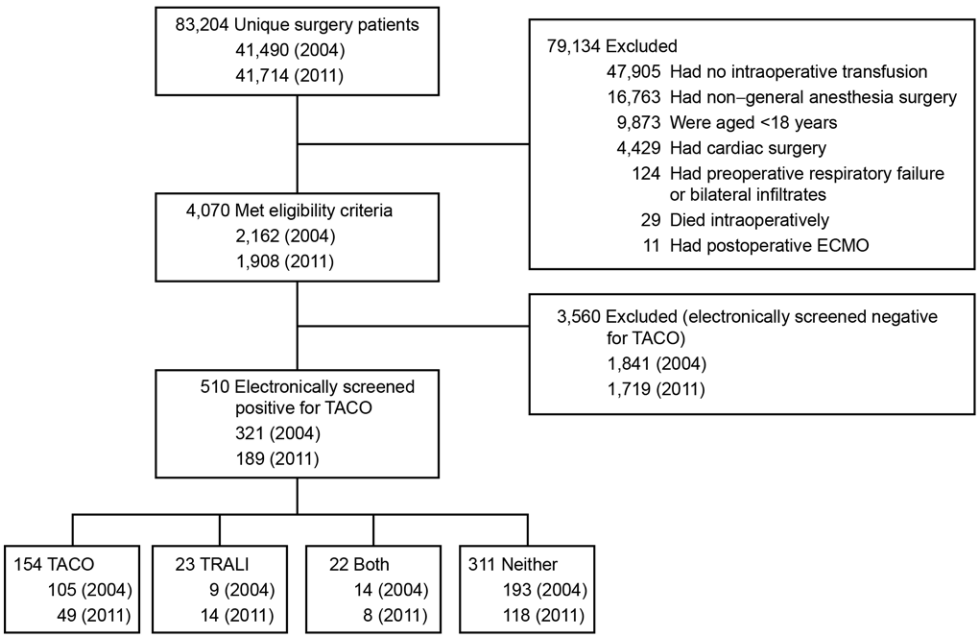

Fig. 1. Patient flowchart. ECMO = extracorporeal membrane oxygenation; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury.

investigation and underwent outcome adjudication using the methods described herein. None of the subjects included in this study were identified from previous studies evaluating the incidence of TRALI and TACO.

Outcome Adjudication

All study participants were screened for the development of TACO using our recently developed natural language processing (NLP)–based electronic screening algorithm (Supplemental Digital Content 1, http://links.lww.com/ALN/B112: TACO screening algorithm).[14] In brief, this screening tool identifies patients with evidence of hypoxemia within 6 h of blood product transfusion and abnormalities consistent with TACO on chest radiographs. The algorithm can detect cases of TACO with a sensitivity and a specificity of 100% (95% CI, 91.4 to 100.0%) and 93.6% (95% CI, 85.0 to 97.6%), respectively.[7,14] The EMRs of all patients who were screened as high probability for TACO by this algorithm were then manually reviewed by two independent physicians (L.C. and Q.J.). A final diagnosis of TACO was determined if patients met at least three of the 2014 criteria established by the National Healthcare Safety Network (table 1).† Our interest in the epidemiology of TACO after intraoperative blood product administration led us to limit outcomes assessments to the 6 h after the last blood product transfusion in the operating room.

If the two reviewing physicians disagreed on a diagnosis, three senior critical care physicians reviewed the case to adjudicate a final outcome. During adjudication, physicians could allocate a diagnosis of TACO as described previously (table 1); TRALI as based on the 2004 Canadian consensus criteria,[15] both, with evidence for both TACO and TRALI, but neither considered sufficient to explain the clinical picture fully, or neither (when case definitions were not met for either TACO or TRALI). Because our primary aim in this investigation was to describe the incidence of TACO in surgical patients, we do not describe cases adjudicated as TRALI here. Of note, these TRALI cases were included in the data set denominator when TACO incidence rates were calculated but were excluded from the analyses evaluating outcomes for TACO cases compared with complication-free transfused patients. Patients considered to have both TRALI and TACO were included in our incidence calculations. Finally, to verify the cases of TACO identified in our study and to evaluate whether our methodology missed any known cases of TACO, we cross-referenced all suspected transfusion reactions reported to the transfusion medicine service with our study population using the FileNet (IBM, Armonk, NY) system maintained at our institution for all suspected transfusion reactions.

Data Sources and Collection

To execute our NLP-based algorithm,[14] we first extracted data used in the algorithm from existing institutional databases. Specifically, unstructured data required for this algorithm—chest radiograph reports obtained within 24 h of the last intraoperative blood product transfusion—were extracted from the enterprise data trust,[12] an institutional warehouse of operational, research, and education databases. Our recently developed NLP procedures were applied to these reports to identify phrases consistent with a diagnosis of TACO. Structured data points that were collected included partial pressure of arterial oxygen (Pa_{O_2}), Pa_{O_2} to fraction of inspired oxygen ratio (Pa_{O_2}:F_{IO_2}), oxygen saturations (Sp_{O_2}), and respiratory rate (Supplemental Digital Content 1, http://links.lww.com/ALN/B112: TACO screening algorithm).[7,14] To ensure completeness, we collected these data from three databases: (1) the perioperative data mart (described above), (2) the ICU data mart[9]—a near real-time database that captures data directly from the EMR for patients in the ICU,[9] and (3) the Mayo Clinic Life Sciences System[11,12]—a repository of replicated data from the EMR of patients admitted to the general surgical floor postoperatively. The sensitivity of our algorithm was maximized by identifying the worst or most extreme values for the patients up to 6 h after blood product transfusion. The most physiologically deranged values were manually verified in the EMR to minimize error. Baseline demographic data were also extracted from the three databases, which have been validated by numerous previous procedures.

Table 1. TACO Definition from the Biovigilance Component of the CDC National Healthcare Safety Network

2010 TACO Criteria
New onset or exacerbation of ≥3 of the following within 6 h of transfusion: • Acute respiratory distress (dyspnea, orthopnea, cough) • Evidence of positive fluid balance • Increased BNP • Radiographic evidence of pulmonary edema • Evidence of left heart failure • Increased CVP

Adapted from Division of Healthcare Quality Promotion; Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component (Internet). Atlanta, GA (2010 July). Available at: http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Accessed May 9, 2014.

BNP = brain natriuretic peptide; CDC = Centers for Disease Control and Prevention; CVP = central venous pressure; TACO = transfusion-associated circulatory overload.

Patient and Transfusion Characteristics

We collected detailed transfusion data using the perioperative information tool, a Microsoft.Net (Microsoft Corp., Redmond, WA) application that contains detailed transfusion information (*e.g.*, exact transfusion times, types of blood products, and volumes). Patient data were extracted from the perioperative data mart, including age, sex, type of surgery, ICU and hospital lengths of stay, and in-hospital mortality status. The automated nature of these validated data extraction procedures helps to ensure optimal data accuracy. This technology has been used previously at our institution to develop screening algorithms for other critical care syndromes with great success.[15–17]

† Available at: http://www.cdc.gov/nhsn/PDFs/Biovigilance/BV-HV-protocol-current.pdf. Accessed May 9, 2014.

Statistics

To evaluate the frequency of TACO after intraoperative blood product transfusion in all eligible patients operated on during 2004 or 2011, we calculated event rates (number of TACO cases/number of encounters) overall and separately for each year. Baseline characteristics are summarized by frequency (percentage) or median (interquartile range [IQR]) for categorical and continuous variables, respectively. Comparison of characteristics between calendar years was carried out using the Wilcoxon rank sum test and the chi-square test, respectively. To assess the relation of various patient and transfusion characteristics on the incidence of TACO, we categorized age, transfusion volume, and fluid balance by quintiles; thereafter, we calculated age-specific, sex-specific, surgical specialty–specific, transfusion volume–specific, and fluid balance–specific rates of TACO for each category (number of TACO cases/number of encounters). Separate univariate logistic regression analyses were performed for each of these characteristics to assess whether the rate of TACO was associated with the given characteristic after adjustment for calendar year. Finally, to assess the clinical significance of a TACO diagnosis in patients compared with other patients in this cohort who did not develop a pulmonary transfusion complication, ICU and postoperative hospital lengths of stay were compared using the *t* test. Patients considered to be transfused controls in this cohort were those who were transfused intraoperatively and did not go on to develop TACO or TRALI. Only patients who went to the ICU were included in the analysis of length of ICU stay. In addition, in-hospital mortality was compared using the chi-square test. Statistical analyses were conducted using the statistical software SAS version 9.1 (SAS Institute Inc.), and *P* values less than 0.05 were considered significant.

Results

We identified 4,070 patients who were eligible for inclusion in this study (2,162 in 2004 and 1,908 in 2011). Table 2

Table 2. Baseline Characteristics of 4,070 Patients by Age, Sex, Transfusion Volume, Fluid Balance, and Surgical Specialty Overall and by Index Year

Characteristics	Overall (N = 4,070)	2004 (n = 2,162)	2011 (n = 1,908)	*P* Value*
Age, median (IQR), yr	65 (53–75)	66 (53–76)	64 (53–74)	0.004
Male sex, No. (%)	2,023 (49.7)	1,057 (48.9)	966 (50.6)	0.27
ASA status, No. (%)				<0.001
I	104 (2.6)	49 (2.3)	55 (2.9)	
II	1,268 (31.2)	601 (27.8)	667 (35.0)	
III	2,272 (55.8)	1,308 (60.5)	964 (50.5)	
IV	399 (9.8)	196 (9.1)	203 (10.6)	
V	26 (0.6)	7 (0.3)	19 (1.0)	
Emergency, No. (%)	477 (11.7)	231 (10.7)	246 (12.9)	0.03
Intraoperative transfusion	4,070 (100)	2,162 (100)	1,908 (100)	
Volume, median (IQR), ml	650 (330–1,025)	600 (350–1,050)	660 (330–996)	0.31
Intraoperative erythrocytes	3,875 (95.2)	2,095 (96.9)	1,780 (93.3)	0.72
Volume, median (IQR), ml	660 (330–996)	600 (350–1,000)	660 (330–993)	0.83
Intraoperative FFP	540 (13.3)	226 (10.4)	314 (16.5)	<0.001
Volume, median (IQR), ml	725 (490–1,326)	860 (500–1,418)	607 (447–1,199)	0.05
Intraoperative platelets	487 (12.0)	210 (9.7)	277 (14.5)	<0.001
Volume, median (IQR), ml	300 (227–562)	300 (253–600)	292 (225–518)	0.03
Intraoperative cryo	134 (3.3)	51 (2.4)	83 (4.4)	<0.001
Volume, median (IQR), ml	208 (194–387)	212 (197–410)	205 (184–382)	0.30
Intraoperative fluid balance, median (IQR), ml	4,180 (2,699–6,154)	4,632 (3,142–6,469)	3,655 (2,200–5,712)	<0.001
Surgical specialty, No. (%)†				<0.001
Abdominal	993 (24.4)	513 (23.7)	480 (25.2)	
OB/GYN	295 (7.2)	157 (7.3)	138 (7.2)	
Neurologic	101 (2.5)	45 (2.1)	56 (2.9)	
Orthopedic	1,005 (24.7)	540 (25.0)	465 (24.4)	
Spine	404 (9.9)	205 (9.5)	199 (10.4)	
Thoracic	138 (3.4)	62 (2.9)	76 (4.0)	
Transplant	193 (4.7)	88 (4.1)	105 (5.5)	
Urology	285 (7.0)	157 (7.3)	128 (6.7)	
Vascular	497 (12.2)	316 (14.6)	181 (9.5)	
Other	159 (3.9)	79 (3.6)	80 (4.2)	

Values are number (%) or median (IQR), unless indicated otherwise. For transfusion volumes, the values presented correspond to the median (IQR) volume transfused in those who received a transfusion of the given product.

* *P* values compare medians and percentages between 2004 and 2011 using the Wilcoxon rank sum test and the chi-square test, respectively. † Percentages for all surgical specialties overall total <100% due to rounding; percentages for all surgical specialties for 2004 total >100% due to rounding.

ASA = American Society of Anesthesiologists; cryo = cryoprecipitate; FFP = fresh-frozen plasma; IQR = interquartile range; OB/GYN = obstetrics and gynecology.

summarizes their baseline characteristics. The median age was 65 yr (IQR, 53 to 75 yr), and patients were marginally older in 2004 (66 *vs.* 64 yr; $P = 0.004$). About half (49.7% [2,023]) were men, which was comparable between calendar years ($P = 0.27$). The median intraoperative transfusion volume was 650 ml (IQR, 330 to 1,025 ml), which was also comparable between calendar years ($P = 0.31$). The median intraoperative fluid balance was 4,180 ml (IQR, 2,699 to 6,154 ml) overall, which was significantly reduced from 2004 (4,632 ml [IQR, 3,142 to 6,469 ml]) to 2011 (3,655 ml [IQR, 2,200 to 5,712 ml]) ($P < 0.001$). Most patients had orthopedic surgeries (24.7% [n = 1,005]) or abdominal surgeries (24.4% [n = 993]); neurologic surgery (2.5% [n = 101]) was the least common. The distribution of patients among surgical specialties between 2004 and 2011 was significantly different ($P < 0.001$); most noticeably, there was a 5.1% reduction in the number of patients undergoing vascular surgeries (14.6% in 2004 *vs.* 9.5% in 2011).

The electronic algorithm identified 510 (12.5%) of the 4,070 patients as having a high probability of TACO (321 in 2004 and 189 in 2011). Manual review showed that 176 (34.5%) of these 510 patients had experienced TACO (agreement by κ statistic, 0.46). One hundred nineteen TACO cases occurred in 2004 (14 of which were considered to have evidence of both TRALI and TACO), and 57 occurred in 2011 (8 of which were considered to have evidence of both TRALI and TACO). Overall, TACO occurred within 6 h of the last intraoperative blood product transfusion at a rate of 4.3% (176 of 4,070 [95% CI, 3.7 to 5.0%]). The incidence of TACO decreased significantly from 5.5% (95% CI, 4.6 to 6.5%) in 2004 to 3.0% (95% CI, 2.3 to 3.9%) in 2011 ($P < 0.001$). This reduction in the rate of TACO was not fully explained by any of the stratified analyses. Specifically, multiple logistic regression analyses revealed a statistically significant reduction in TACO from 2004 to 2011 even after adjustment for variation in age ($P < 0.001$), sex ($P < 0.001$), type of surgery ($P = 0.002$), transfusion volume ($P < 0.001$), and fluid balance ($P = 0.005$; table 3). Multivariable logistic regression models evaluating product-specific rates of TACO between 2004 and 2011 demonstrate significantly different rates of TACO by both blood product ($P < 0.001$) and year ($P < 0.001$) (table 4). Overall, the highest incidence rate of TACO occurs in patients receiving mixed blood products (73 of 564 [12.9%]), closely followed by patients receiving fresh-frozen plasma only (11 of 93 [11.8%]). In 2004, fresh-frozen plasma had the highest incidence rate of TACO (7 of 34 [20.6%]), with an absolute reduction in number of events between the 2 calendar years; this was surpassed by mixed blood products in 2011 (35 of 321 [10.9%]) (table 4).

After adjustment for the reduction in TACO between 2004 and 2011, the difference in the rate of TACO between men and women was no longer significant (4.8% [95% CI, 4.0 to 5.9%] *vs.* 3.8% [95% CI, 3.1 to 4.7%]; $P = 0.09$). However, the rates of TACO by type of surgical procedure remained significant ($P < 0.001$). Overall, vascular (12.1% [95% CI, 9.5 to 15.2%]), transplant (8.8% [95% CI, 5.6 to 13.7%]), and thoracic surgeries (7.2% [95% CI, 4.0 to 12.8%]) had the highest TACO rates, whereas obstetric and gynecologic surgical patients had the lowest rates (1.4% [95% CI, 0.5 to 3.4%]). The rate of TACO increased with increasing age ($P < 0.001$), with the rate in patients aged 80 yr or older (7.4% [95% CI, 5.2 to 9.6%]) almost quadruple that observed in patients aged 49 yr or younger (2.0% [95% CI, 1.1 to 3.1%]), double that in patients aged 60 to 69 yr (4.2% [95% CI, 2.9 to 5.4%]), and 1.5 times that in patients aged 70 to 79 yr (5.2% [95% CI, 3.8 to 6.6%]). We also observed an increased rate of TACO with increasing amount of volume transfused ($P < 0.001$) and increasing total fluid balance ($P < 0.001$).

Importantly, of the 176 cases of TACO identified during the 2-yr study period, only 3 were included in the transfusion medicine service's database of potential transfusion reactions. In all three cases, the investigation into a potential transfusion reaction was unrelated to blood products administered in the operating room. Furthermore, none were identified as a TACO reaction. This once again highlights the lack of clinical recognition of TACO and the rationale for this study. However, we did observe important differences in outcomes of patients who developed TACO compared with their complication-free transfused counterparts. Specifically, TACO cases had a median postoperative ICU length of stay of 10.8 days (IQR, 4.2 to 30.8 days) compared with just 5.7 days (IQR, 2.7 to 14.8 days) for transfused controls ($P < 0.001$). Similarly, for postoperative hospital length of stay, TACO cases had a median of 11.6 days (IQR, 7.3 to 22.3 days) compared with just 6.2 days (IQR, 4.2 to 9.3 days) for transfused controls ($P < 0.001$). Finally, evaluation of in-hospital mortality showed that, of the 176 patients with TACO, 15 died (8.5%) compared with 93 of the 3,894 transfused controls (2.4%). This resulted in an odds ratio of death for TACO cases compared with transfused controls of 3.8 (95% CI, 2.2 to 6.7) ($P < 0.001$).

Discussion

Our findings provide detailed descriptive data on the incidence rates and characteristics of patients with perioperative TACO. The use of our recently developed NLP-based algorithm enabled us to capture what we believe to be a more representative sample of surgical patients experiencing TACO and therefore to better define its true incidence in this population. This retrospective cohort study of 4,070 noncardiac surgical patients confirms an overall rate of TACO of 4.3% (95% CI, 3.7 to 5.0%). Although this overall incidence for both years of the study is consistent with that reported previously in other patient populations,[3,5] the incidence from 2004 to 2011 did decrease significantly (from 5.5 to 3.0%; $P < 0.001$). Increased rates of TACO were associated with surgical specialty, increased transfusion volume, and total operative fluid balance (all $P < 0.001$). However, the declining incidence of TACO was not fully accounted for by any patient or transfusion characteristics.

Table 3. Incidence Rates of Perioperative Transfusion-associated Circulatory Overload by Subgroup Overall and by Index Year

	Overall No./Total (%)	2004 No./Total (%)	2011 No./Total (%)	*P* Value
Overall	176/4,070 (4.3)	119/2,162 (5.5)	57/1,908 (3.0)	<0.001*
Age, yr				
≤49	16/779 (2.1)	10/414 (2.4)	6/365 (1.6)	
50–59	23/699 (3.3)	13/345 (3.8)	10/354 (2.8)	<0.001†
60–69	42/1,005 (4.2)	22/500 (4.4)	20/505 (4.0)	
70–79	53/1,019 (5.2)	39/572 (6.8)	14/447 (3.1)	<0.001*
≥80	42/568 (7.4)	35/331 (10.6)	7/237 (3.0)	
Sex				
Male	98/2,023 (4.8)	62/1,057 (5.9)	36/966 (3.7)	0.09†
Female	78/2,047 (3.8)	57/1,105 (5.2)	21/942 (2.2)	<0.001*
Surgical specialty				
Abdominal	42/993 (4.2)	27/513 (5.3)	15/480 (3.1)	
OB/GYN	4/295 (1.4)	4/157 (2.5)	0/138 (0.0)	
Neurologic	4/101 (4.0)	3/45 (6.7)	1/56 (1.8)	<0.001†
Orthopedic	22/1,005 (2.2)	18/540 (3.3)	4/465 (0.9)	
Spine	6/404 (1.5)	5/205 (2.4)	1/199 (2.3)	
Thoracic	10/138 (7.2)	6/62 (9.7)	4/76 (5.3)	
Transplant	17/193 (8.8)	8/88 (9.1)	9/105 (8.6)	0.001*
Urology	7/285 (2.5)	4/157 (2.5)	3/128 (2.3)	
Vascular	60/497 (12.1)	42/316 (13.3)	18/181 (9.9)	
Other	4/159 (2.5)	2/79 (2.5)	2/80 (2.5)	
Transfusion volume, ml				
≤350	22/1,353 (1.6)	16/682 (2.3)	6/671 (0.9)	
351–700	44/1,279 (3.4)	32/719 (4.5)	12/560 (2.1)	<0.001†
701–1,050	19/487 (3.9)	16/262 (6.1)	3/225 (1.3)	
1,051–1,400	17/289 (5.9)	13/172 (7.6)	4/117 (3.4)	<0.001*
≥1,401	74/662 (11.2)	42/327 (12.8)	32/335 (9.6)	
Fluid balance, ml				
≤2,000	13/601 (2.2)	8/186 (4.3)	5/415 (1.2)	
2,001–4,000	32/1,325 (2.4)	23/682 (3.4)	9/643 (1.4)	<0.001†
4,001–6,000	43/1,065 (4.0)	31/656 (4.7)	12/409 (2.9)	
6,001–8,000	28/558 (5.0)	20/340 (5.9)	8/218 (3.7)	0.005*
≥8,001	60/521 (11.5)	37/298 (12.4)	23/223 (10.3)	

Multiple independent logistic regression analyses were performed for each patient characteristic to evaluate the difference in rate of transfusion-associated circulatory overload.

* *P* value for the difference in the rate of transfusion-associated circulatory overload by year (from 2004 to 2011), after adjustment for the variation in rate by each characteristic. † *P* value for the difference in the rate of transfusion-associated circulatory overload by characteristic, after adjustment for the variation in rate by year (from 2004 to 2011).

OB/GYN = obstetrics and gynecology.

Table 4. Product-specific Incidence Rates of Perioperative Transfusion-associated Circulatory Overload Overall and by Index Year

	Overall No./Total (%)	2004 No./Total (%)	2011 No./Total (%)
Erythrocytes only	90/3,322 (2.7)	74/1,853 (4.0)	16/1,469 (1.1)
FFP only	11/93 (11.8)	7/34 (20.6)	4/59 (6.8)
Platelets only	2/89 (2.2)	0/32 (0.0)	2/57 (3.5)
Mixed products	73/564 (12.9)	38/243 (15.6)	35/321 (10.9)

Multivariable logistic regression analyses demonstrated that the frequency of transfusion-associated circulatory overload was related to both blood product group ($P < 0.001$) and calendar year ($P < 0.001$). Two patients were excluded from this secondary analysis (one received only fresh whole blood and one received only cryoprecipitate; neither experienced transfusion-associated circulatory overload).

FFP = fresh-frozen plasma.

To better understand the epidemiology of TACO in patients cared for by anesthesia providers, we studied only those surgical patients who were transfused in the operating room. Our primary reasons for selecting this population are that a large proportion of blood product transfusions take place in the operating room environment[18] and that a substantial proportion of those who experience TACO will do so after intraoperative transfusion (70% of all TACO

episodes).[7] Notwithstanding the findings of a few studies,[2,16] most investigations to date have focused on the epidemiology of TACO in the critically ill.[3,5] How well these results apply to most patients encountered in the operating room is unclear. Historically, incidence rates have ranged from less than 1 to 11%.[3,5] One of the earliest studies investigating TACO in surgical populations in the mid-1990s found it to be a "frequent and serious event in orthopedic surgery," occurring at a rate of 1.05%.[2] A decade later, the same authors reported rates of TACO ranging from 1 to 8% in patients undergoing hip or knee surgery.[16] More recently, a 2011 report from a single-center prospective cohort study documented an incidence of 6% in the ICU.[3]

The reasons for this variation in TACO incidence rates are likely multifactorial, explained in part by differing populations, definitions of TACO, case adjudication strategies, and study designs. However, none of these studies addressed the specific objective of our study—to define the incidence of TACO in noncardiac surgical populations. We believe that the use of our novel, highly sensitive NLP-based screening algorithm, combined with the detailed manual review of a large number of transfused surgical cases from 2 different calendar years, produced results that likely provide a more accurate reflection of the true incidence of TACO and are thus also broadly generalizable to noncardiac surgical populations.

Interestingly, in the current study, we observed a significant reduction in the rate of TACO between 2004 and 2011. Moreover, this decline in incidence was not fully explained by any of the patient and transfusion characteristics evaluated in this study. Although the introduction of male-only plasma has been accepted as resulting in a reduced rate of TRALI during this time period,[18] until recently no hypotheses existed to explain similar reductions in the incidence of TACO as perhaps resulting from changes in blood product procurement strategies. The pathophysiologic mechanisms underlying TACO have largely been considered to be due to volume overload. In this context, there is little biologic rationale to explain why the exclusion of female plasma donors would affect the rates of TACO. Interestingly, additional changes in blood management have also taken place during this interval. For example, our institution implemented universal leukoreduction in 2005. Blumberg *et al.*[19] recently described a 49% reduction in the rate of TACO after universal leukoreduction. This finding was largely attributed to a reduction in TACO related to erythrocyte units rather than other components. Blumberg *et al.*[19] hypothesized that TACO may therefore not be solely explained by volume overload but instead may also have an inflammatory/immunologic component. They highlighted the possible role of leukocyte-derived microparticles and other mediators of capillary leak that accumulate during storage. Although data from this observational study cannot be used to imply causality, our findings suggest that this potential mechanism may warrant further investigation. Future studies should be designed and powered to evaluate the potential role of leukoreduction while accounting for other potential confounding variables and changes in clinical practice that have occurred during the same period.

Although the sensitivity of our electronic screening algorithm was previously demonstrated to be 100%,[14] the decision to limit manual review to patients who screened as high probability for TACO with the electronic algorithm may have resulted in missed cases. For example, a patient with three or more U.S. Centers for Disease Control and Prevention criteria for TACO may have been missed because of the absence of infiltrates on chest radiographs or the hypoxemia criteria used in our screening algorithm. This in addition to our exclusion of patients with preexisting respiratory failure and/or pulmonary infiltrates on chest radiographs may have resulted in an underestimation of the true incidence of TACO. Nonetheless, although our estimates may be conservative, we believe that the strategies implemented for TACO adjudication in this investigation likely remain a significant improvement upon past efforts aiming to detect TACO, which have primarily relied on manual detection alone.[7] In addition, we would also emphasize that the algorithm did not miss any cases of TACO that were reported to the transfusion medicine service during the defined study period.

In addition to the limitations noted above, we further acknowledge that our study population was derived from a single tertiary care referral center. It is possible that referral bias may affect the reported incidence of TACO because we selected patients with a higher prevalence of comorbid conditions than that of surgical populations seen in nonreferral centers. Similarly, results obtained in the current study cannot be generalized to patients receiving nongeneral anesthesia, as this subset of patients was not included in our study cohort. Indeed, external validation of our findings will require further study.

Finally, this study was designed as a descriptive cohort study with the aims of more accurately defining the incidence of TACO after noncardiac surgery and describing it in the context of a limited number of patient and transfusion characteristics. The investigation was not designed to extensively evaluate specific risk factors for TACO or its attributable burden. Thus, although associations were noted between such characteristics and the development of TACO, more robust and definitive evaluations of TACO risk factors will require future study. Similarly, although associations were noted between TACO and adverse patient-important outcomes such as prolonged ICU and hospital length of stay and increased mortality, these findings were not adjusted for severity of illness of other potentially confounding variables. These findings are presented primarily to highlight the fact that cases of TACO identified in this study but missed by the clinical practice do not appear to be clinically insignificant. However, as with the evaluation of risk factors for TACO, a more comprehensive understanding of the true impact of TACO on patient-important outcomes as compared with

outcomes for complication-free transfused patients will require additional study, with fully adjusted analyses.

In conclusion, there remain significant barriers to the accurate characterization of the epidemiology of TACO, particularly in surgical populations. Herein, we demonstrate a recent estimate of the incidence of TACO in surgical populations to be 3.0%, with a significant reduction in the rate of TACO from 2004 and 2011, that was not fully explained by either patient or transfusion characteristics evaluated in this study. This robust characterization of the epidemiology of TACO in surgical populations should (1) heighten the awareness of transfusion risks among perioperative healthcare providers, (2) facilitate improved decision making regarding transfusion strategies in at-risk patients, and (3) enhance the timely implementation of appropriate treatment interventions for this serious transfusion-related pulmonary complication. Future studies will more completely define the true attributable burden, the underlying mechanisms, and the risk factors for TACO. Furthermore, with improved understanding of the risk factors underlying TACO, we would expect to be able to refine the electronic algorithm used to screen patients in this study, developing a real-time prediction and/or prevention model for TACO that may help to mitigate its incidence.

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Competing Interests

The authors declare no competing interests.

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