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Risk Factors and Clinical Outcomes Associated with Perioperative Transfusion-Associated Circulatory Overload

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Abstract

Background—Transfusion-associated circulatory overload (TACO) remains under-appreciated in the perioperative environment. We aimed to characterize risk factors for perioperative TACO and better understand its impact on patient-important outcomes.

Methods—In this case-control study, 163 adults undergoing non-cardiac surgery who developed perioperative TACO were matched with 726 transfused controls who did not develop respiratory complications. Univariate and multivariable logistic regression analyses were used to evaluate potential risk factors for TACO. The need for postoperative mechanical ventilation, lengths of intensive care unit (ICU) and hospital stay and mortality were compared.

Results—For this cohort, the mean age was 71 years and 56% were male. Multivariable analysis revealed the following independent predictors of TACO: emergency surgery, chronic kidney disease, left ventricular dysfunction, prior beta-adrenergic receptor antagonist use, isolated fresh frozen plasma transfusion (versus isolated erythrocyte transfusion), mixed product transfusion (versus isolated erythrocyte transfusion), and increasing intraoperative fluid administration. Patients who developed TACO were more likely to require postoperative mechanical ventilation (73% versus 33%; $p < 0.001$) and experienced prolonged ICU (11.1 versus 6.5 days; $p < 0.001$) and hospital lengths of stay (19.9 versus 9.6 days; $p < 0.001$). Survival was significantly reduced ($p < 0.001$) in transfusion recipients who developed TACO (1-year survival 72% versus 84%).

Conclusions—Perioperative TACO was associated with a protracted hospital course and increased mortality. Efforts to minimize the incidence of TACO should focus on the judicious use of intraoperative blood transfusions and non-sanguineous fluid therapies, particularly in patients with chronic kidney disease, left ventricular dysfunction, chronic beta-blocker therapy, and those requiring emergency surgery.

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Introduction

Approximately 30 million allogeneic blood components are transfused annually in the United States (US)¹, with perioperative transfusions accounting for approximately 25% of these². Notably, the incidence of transfusion-related infectious complications has fallen dramatically³. As a result, many consider transfusion therapies to be “safer than ever”^{4,5}. However, the frequency and impact of non-infectious complications such as transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) have been increasingly described and appreciated^{6–14}. Indeed, TACO has been identified as a major area of interest for national research networks such as the National Heart Lung and Blood Institute-funded Recipient Epidemiology and Donor Evaluation Survey III research network¹⁵.

Characteristically described as a syndrome of acute respiratory distress with tachycardia and hypertension following blood product administration, formal criteria for TACO have only recently been endorsed. The two most widely accepted definitions include those put forth by the National Healthcare Safety Network and the International Society of Blood Transfusion (Table 1)^{16,17}. Both of these criteria require a new onset or worsening of respiratory distress within six hours of completion of blood product transfusion and include parameters for fluid balance, evidence of heart failure and radiographic evidence of circulatory overload. The International Society of Blood Transfusion definition includes additional hemodynamic vital sign parameters consistent with circulatory overload.

Historically, TACO has been estimated to occur in approximately 1% to 10% of all transfused patients^{18–20}. More recently, it was suggested to occur in 3% to 5.5% of transfused non-cardiac surgical patients⁶. Importantly, TACO was the second leading cause of transfusion-related fatalities in the US in 2014 accounting for 22% of all transfusion-related deaths reported to the Food and Drug Administration (FDA)³. Meanwhile, in 2013, TACO accounted for 55% of all transfusion-related fatalities reported to the Serious Hazards of Transfusion group in the United Kingdom²¹. TACO also appears to be dramatically under-reported^{6,22,23}.

Although the risk factors and clinical impact of TACO have previously been explored in heterogeneous hospitalized cohorts⁸, a contemporary evaluation of such risk factors in a well defined surgical population remains heretofore outstanding. In an effort to more fully inform the practice of perioperative transfusion medicine, we aimed to further clarify the risk factors underlying perioperative TACO in patients undergoing non-cardiac surgical procedures. Moreover, we aimed to improve our understanding of the impact of postoperative TACO on patient-important outcomes.

Materials and Methods

Study Design

This investigation utilized a case-control study design. All patients included in this study had valid research authorization. The study was approved by the Mayo Clinic Institutional Review Board, 200 First Street SW, Rochester, MN, USA, prior to its onset. The

Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed in the conduct and reporting of this study²⁴.

Study Population

One hundred and sixty three cases of TACO were matched with up to 5 transfused and complication free controls (n = 726). Patients were matched on age (+/- 5 years), sex, surgical specialty and year of surgery. Matching based upon surgical procedure was pursued as a result of our recent work suggesting that a significant proportion of TACO cases occur in patients undergoing thoracic, vascular and transplant surgery⁶. Matching based upon this variable was pursued with the aim of removing this risk factor as a confounder of additional risk factors of interest. Similarly, age and sex have previously been shown to be strongly associated with TACO in non-surgical populations^{10,13,18,25,26}. Cases and controls were both selected from a cohort of adult patients recently identified at our institution who were transfused while undergoing non-cardiac surgery in the calendar years 2004 or 2011⁶. These calendar years were specifically chosen in our original epidemiologic study, as they represent periods before and after the introduction of 2 major blood managements strategies at our institution, universal leukoreduction and deferral of female plasma donors. Exclusion criteria for the original cohort included the lack of research authorization; previous inclusion in the study (no patient was included more than once); age <18 years; pre-transfusion evidence of respiratory failure, extracorporeal membrane oxygenation or diffuse bilateral infiltrates on chest radiographs; American Society of Anesthesiologists physical status classification VI; or intraoperative death. The remaining patients in this cohort underwent an extensive evaluation for evidence of transfusion-related pulmonary complications within 6 hours of intraoperative transfusion as was previously described⁶. For consistency, the National Healthcare Safety Network definition was used to identify cases of TACO¹⁶. Additional outcome adjudication categories included TRALI, defined as either TRALI, or possible TRALI (otherwise known as transfused acute respiratory distress syndrome) according to the 2004 consensus conference definition²⁷; mixed TRALI and TACO, when evidence for both existed; or control if neither TRALI or TACO were identified. For the present investigation, those with either TACO or mixed TRALI/TACO were compared to controls. Those with isolated TRALI were excluded.

Data Collection

Variables considered as potential risk factors for TACO were identified based upon biologic plausibility and by review of the available literature^{8,13,18,25,26}. These elements were extracted from the electronic medical record (EMR) using institutional databases that have been previously validated^{28,29}. These data included age; sex; type of surgery; year of surgery; type and volume of blood products transfused; intraoperative fluid administration; preoperative hemoglobin values; estimated blood volume; body mass index (BMI); estimated blood loss; duration of surgery; documented history of congestive heart failure (CHF), coronary artery disease or prior myocardial infarction, chronic kidney disease (CKD), moderate to severe liver disease, or alcohol abuse; echocardiographic evidence of left ventricular (LV) dysfunction, evidenced by ejection fraction <60%, early diastolic mitral inflow velocity to early diastolic mitral annulus velocity >15 or documented grade 3–4/4 diastolic dysfunction; and preoperative use of aspirin, diuretics or beta-adrenergic receptor

antagonists (β -blockers). Preoperative use of the medications of interest was defined as documented ongoing usage in the six-month interval preceding surgery. American Society of Anesthesiologists (ASA) physical status classification was extracted to further demonstrate the characteristics of our study population. When building our models, ASA status was not evaluated as a specific risk factor due to our desire to focus more specifically on individual comorbidities and the problems with co-linearity and over fitting of models that might occur should these comorbidities and ASA status both be included in our model. The patient-important outcomes evaluated included intensive care unit (ICU) and hospital length of stay, need for postoperative mechanical ventilation, and survival following the index surgical procedure. Dates of death and last follow-up were obtained using institutional resources.

Statistical Analysis

The baseline characteristics of our study sample are presented as median and interquartile range for continuous variables and number (%) for binary or categorical data. The association of each characteristic with TACO was assessed using univariate conditional logistic regression analysis in order to account for the matching procedures with SAS statistical software version 9.1 (SAS Institute Inc, Cary NC). In addition to these unadjusted analyses, each risk factor was also assessed using multivariable conditional logistic regression with intraoperative blood volume and non-sanguineous intravascular (IV) fluid volume included as covariates to account for the vastly differing volume of these products administered intraoperatively between groups. Co-linearity was assessed at multiple points while building our multivariable model using variance inflation factors for each variable included in the model. Variables that remained significant predictors of TACO following the fluid volume-adjusted analyses ($p < 0.05$) were chosen for inclusion in a final multivariable conditional logistic model. Finally, subset analyses were carried out, excluding patients with evidence of both TRALI and TACO in order to ensure that our findings were not confounded by this particular group of patients in whom a differing phenotype may be expected. In all cases findings are summarized by presenting the odds ratio (95% confidence interval (CI)) and corresponding two-tailed p-value. The sample size for this study was based upon available data, with no a priori power calculation being performed. To maximize the power of this study, 1:5 matching of cases to controls was utilized. Caution was taken to avoid over fitting models by evaluating no more than 1 variable per 10 observations (cases of TACO). Supplemental analyses were performed to compare clinical outcomes within subgroups. Need for postoperative mechanical ventilation is summarized as number (%) and compared between groups using conditional logistic regression with preoperative ASA status included as a covariate in order to account for chronic comorbidities and acuity of illness. Postoperative survival is summarized with hazard ratios (95% CI) and corresponding p-value using the Kaplan Meier method and analyzed using stratified Cox proportional hazards regression taking into account the matched set study design and with preoperative ASA status included as a covariate. Postoperative ICU and hospital lengths of stay are displayed as median and interquartile range, and analyzed using quantile regression with matching variables and ASA status included as covariates. Findings were considered statistically significant where $p < 0.05$.

Results

A total of 52,139 adult patients underwent non-cardiac surgery with general anesthesia at our institution during the years 2004 and 2011. Of these, 4,234 received intraoperative transfusion. After exclusion criteria were applied, 4,070 patients were evaluated for evidence of perioperative transfusion-related pulmonary complications. From this cohort, 154 patients were found to have TACO, 23 patients were found to have TRALI, and 22 patients were felt to have evidence for both TRALI and TACO. A total of 3,871 had no evidence of post-transfusion pulmonary compromise⁶. From the cohort of 176 patients with evidence of TACO, 163 cases were successfully matched with up to 5 complication-free transfused controls (n = 726) making up the participants of this case-control study. For 13 cases, no suitable controls were able to be identified from our cohort due to the absence of a matching procedural code. Of these 13 patients, 11 had TACO alone, while 2 had evidence of TRALI and TACO, 7 (54%) were male, 7 (54%) underwent surgery of interest in 2004, the mean age was 74 years, 2 patients were undergoing orthopedic surgery, 5 were undergoing vascular surgery, 5 were undergoing general surgery, and 1 was undergoing neurosurgery. Overall, 123 patients were successfully matched with 5 controls, 10 patients were matched with 4 controls, 17 were matched with 3 controls, 7 were matched with 2 controls and 6 were matched with only 1 control.

Baseline characteristics are shown in Table 2. Matching was successful with no significant differences between cases and controls with regard to age, sex, type of surgery or surgical year (all $p > 0.05$). Patients with TACO were more likely to have preoperative echocardiographic evidence of LV dysfunction. In addition, they were more likely to have a higher BMI, pre-existing CKD and be using diuretics or β -blockers in the 6 month period prior to surgery. Patients with TACO were also more likely to present for emergency surgery, have a longer duration of surgery, and received greater volumes of blood products, as well as non-sanguineous IV fluids. Patients who developed TACO were more likely to receive plasma or mixed product transfusion episodes rather than isolated RBC transfusions. In contrast, controls were more likely to receive isolated RBC transfusions. None of the TACO cases received platelet transfusions in isolation. Preoperative hemoglobin values were statistically lower in patients with TACO, but this difference did not appear to be clinically significant. There were no significant between-group differences in estimated blood volume, coronary artery disease, clinical notes documenting CHF or liver disease, alcohol abuse or preoperative aspirin use (Table 2). Missing data were similar for both cases and control, and are outlined in Table 2.

Due to a significant association between TACO and both intraoperative transfusion and non-sanguineous IV fluid volumes, analyses were adjusted for these volumes in an effort to control for their confounding effects (Table 3). After adjusting for total fluid volumes, TACO remained associated with emergency surgery, CKD, echocardiographic evidence of LV dysfunction, lower preoperative hemoglobin, preoperative diuretic administration, and preoperative β -blocker use (Table 3). In addition, patients with TACO were more likely to have received either plasma only or mixed blood product transfusion episodes as compared to isolated RBC transfusion (Table 3). No evidence of co-linearity was detected, with a maximal variance inflation factor of 1.74. In these adjusted analyses, there was no longer a

significant relationship between TACO and duration of surgery or BMI. Similarly, no association was demonstrated between TACO and clinical documentation of CHF, coronary artery disease, moderate to severe liver disease, alcohol abuse, estimated blood volume, estimated blood loss or preoperative aspirin use (Table 3).

Table 3 displays the results of the multivariable analysis modeling the relationships between variables identified as having a statistically significant association with TACO in the fluid volume-adjusted analyses and the outcome of TACO. This final multivariable model demonstrated statistically significant relationships between TACO and emergency surgery; chronic kidney; echocardiographic evidence of LV; preoperative β -blocker utilization; blood product type, plasma and mixed blood products (both $p = 0.011$) and increasing IV fluid volume. Transfusion volume, diuretic use and preoperative hemoglobin were no longer statistically significant in the final multivariable model (Table 3).

In terms of the patient-important outcomes assessed in this investigation, patients who developed perioperative TACO (when compared to controls) following intraoperative blood product transfusion had a significantly greater need for postoperative mechanical ventilation (73.0 % vs. 33.2 %, $p < 0.001$). Of those patients requiring postoperative ICU care [TACO $n = 161$ (98.8 %), controls $n = 520$ (71.6 %)], ICU length of stay was significantly increased in the TACO cohort [11.1 days (95% CI 4.3 – 30.5) vs. 6.5 days (95% CI 2.9 – 19.1), covariate adjusted $p < 0.001$]. Postoperative hospital length of stay was also significantly longer in those who experienced perioperative TACO [12 days (95% CI 7 – 22) vs. 5 days (95% CI 7 – 10), covariate adjusted $p < 0.001$]. Moreover, survival was notably reduced in those who experienced perioperative TACO (hazard ratio = 2.1, 95% C.I. 1.7 to 2.4, $p < 0.001$) (Figure. 1, Table 4).

Subset analyses performed after excluding patients with evidence of TRALI showed no significant differences in baseline characteristics (see table supplemental digital content 1), univariate (see table supplemental digital content 2) or multivariate models (see table supplemental digital content 3).

Discussion

In this study, we have demonstrated that premorbid conditions (CKD, LV dysfunction), baseline medications (β -blockers), procedural details (emergency surgery), intraoperative care delivery factors (increasing IV non-sanguineous fluid volume), and blood product type (plasma or mixed product transfusion episodes) are independently predictive of perioperative TACO. A number of these findings are consistent with risk factors previously described in heterogeneous patients populations^{8,13,30}. Uniquely, we have demonstrated an increased risk of TACO in those coming to emergency surgery. Of interest, we failed to demonstrate a relationship between blood product volume and TACO, after adjusting for other variables including non-sanguineous fluid balance and blood product type. Importantly, the presence of TACO negatively impacted patient-important outcomes with increased need for postoperative mechanical ventilation, increased ICU and hospital lengths of stay and significantly reduced short and long-term survival.

Our findings of increased rates of TACO in those with CKD, echocardiographic evidence of LV dysfunction, preoperative β -blocker use and greater volumes of IV fluid administration all support the notion that *volume overload and hydrostatic pulmonary edema* are central processes in TACO pathogenesis. The consistency with which these parameters have been associated with TACO in the literature supports the judicious use of blood product transfusion – and careful management of overall volume status – especially in patients with preexisting cardiac and renal dysfunction. Although the precise mechanisms underlying TACO remain under investigation, specifically with regard to the potential role of inflammatory or non-cardiogenic pulmonary edema, and while TACO may still occur even with conservative IV fluid administration, careful volume management would seem prudent regardless of etiology, since patients with increased capillary leak are also likely susceptible to pulmonary edema with increasing IV fluid administration. Interestingly, clinical documentation of CHF was not found to be a significant predictor of TACO in this study. Notably, 107 patients with echocardiographic evidence of either LV systolic or diastolic dysfunction within 6 months prior to surgery did not have CHF documented in their clinical notes. Similarly, 36 patients with clinical documentation of CHF had a normal echocardiogram in the six month interval prior to their surgical procedure. On this basis, we believe objective echocardiographic abnormalities may be a more sensitive and specific marker of LV dysfunction and risk for TACO than relying upon prior clinical documentation of CHF.

The association of preoperative β -blocker administration with risk for postoperative TACO is a novel study finding. We suspect that preoperative β -blocker use likely serves as a surrogate marker for cardiovascular disease and left ventricular dysfunction with the associated risk for developing TACO. Alternatively, patients taking β -blockers may be less well equipped to deal with acute intravascular volume expansion. Regardless, the observational nature of this investigation precludes definitive statements on the underlying pathophysiologic rationale relating β -blocker therapy to increased risk for postoperative TACO.

Receipt of either plasma products alone or mixed blood products remained independent predictors of TACO when compared to those who received RBCs exclusively. This relationship appeared robust, persisting after adjusting for intravenous fluid volume administration. This finding, combined with the fact that transfusion volume was not associated with TACO in the multivariable model, supports the potential for alternate mechanisms contributing to TACO pathogenesis – such as inflammatory processes. Notably, others have also identified this association. In 2011, Li et al. reported that plasma prescribed for the correction of an elevated international normalized ratio was strongly associated with TACO in the critically ill¹⁸. Similarly, in 2012, Narick and colleagues reported an incidence of TACO attributable to plasma of 4.8% in the non-operative setting²³. Interestingly, these authors noted lower plasma infusion volumes and infusion rates in those who developed TACO when compared to those who did not develop this complication. This again raises the possibility of additional mechanisms underlying TACO beyond fluid overload.

The supposition that TACO may not be purely driven by volume overload was suggested by Popovsky et al. in 2010³¹ when it was noted that TACO frequently occurred after 1–2 blood

component transfusions, a volume that would not typically cause clinically significant fluid overload. Subsequently, Andrzejewski et al. reported approximately 65% of patients with TACO exhibited an inflammatory or febrile component with their clinical presentation^{32,33}. Similar findings were also reported by the Quebec Hemovigilance System³⁴. Observations such as these suggest the potential for inflammatory mechanisms contributing to TACO pathogenesis. A growing body of pre-clinical investigations have also suggested a potential role for RBC-derived microparticles, cell free hemoglobin and nitric oxide scavenging as a potential mechanism associated with TACO pathogenesis^{35–38}. Clinically, this mechanism may underlie the characteristic hypertensive response seen in TACO. An additional observation suggesting the potential for alternate mechanisms underlying TACO pathogenesis is the notable lack of TACO in patients receiving washed cellular blood products³⁹. Though the present study is unable to sufficiently address these hypotheses, evidence suggests further investigation may be warranted. Indeed, an NIH-funded clinical trial investigating this possibility remains underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02094118) ID: NCT02094118).

Our finding of an association between emergency surgery and TACO, though unique, is not entirely unforeseen. Indeed, in the cohort from which study participants were identified, it was noted that TACO was significantly more frequent amongst patients undergoing vascular, thoracic and organ transplantation surgery. It is presumed that these patients are more likely to carry sinister comorbidities and more frequently require transfusion therapies. In light of this fact, we matched patients in the present investigation on type of surgery, thereby permitting an evaluation of other important predictors of TACO without such confounding. However similar assertions could also be made about emergency surgery. By nature, these patients are presumed to be acutely unstable. Of note, a recent report from Murphy et al. suggested that surgery within 48 hours of a transfusion episode, particularly cardiac, liver and vascular surgery, were predictors of TACO⁸. Though this association lost statistical significance in Murphy's multivariable analysis, it must be acknowledged that the cohort was very different from the present study. Specifically, their population included surgical and medical inpatients, the critically ill and transfused outpatients.

Amongst patients developing TACO, the need for postoperative mechanical ventilation, as well as the ICU and hospital lengths of stay were significantly increased – a finding that has been consistently duplicated in other investigations. Likewise, both short and long-term survival were noticeably reduced in patients with TACO. Similar associations attesting to the negative impact of TACO on patient-important outcomes have been described since the early 1990s³⁰, however some reports have failed to duplicate these findings^{28, 17, 40}. The negative impact of TACO on patient-important outcomes was most recently endorsed by Murphy et al.⁸. It should be noted that TACO remains a leading cause of transfusion related fatalities worldwide^{3,21,34}. As such, measures aiming to prevent TACO, especially in high risk populations, should be employed in the perioperative period.

Our study has a number of strengths that deserve mention. Firstly, cases and controls were selected from a previously collected database of transfusion recipients who had undergone rigorous review for the outcome of TACO⁶. As such, we believe the findings described herein are truly representative of patients experiencing perioperative TACO. Secondly, relevant risk factors were extracted from the EMR using tools that have previously

undergone extensive validation^{28,41–43}. There are also several weaknesses that must be acknowledged. First, the observational nature of this study creates potential for confounding and bias. Although efforts were made to control for these issues in both the study design and statistical analyses, potential for unmeasured confounding effects clearly remains. If present, residual confounding has the potential to impact associations between the risk factors evaluated and TACO, as well as the associations with patient-important outcomes. The conduct of this study at a single tertiary care academic medical center is an additional limitation. Unique aspects relating to the patient's cared for at this institution or the care delivered may preclude generalization of our results to patients at disparate institutions. External validation would greatly enhance the robustness of our findings. Finally, additional risk factors should be considered in future studies. As an example, the rate of transfusion administration – a risk factor reported in the literature¹⁸ – could not be evaluated in the present study as this data was not reliably available for all patients receiving intraoperative transfusions.

In summary, perioperative TACO is independently associated with CKD, LV dysfunction, pre-surgical β -blocker use, increasing intraoperative fluid administration, and emergency surgery. Until targeted therapies are available to treat TACO, prevention remains paramount with the avoidance of unnecessary transfusions being critically important. Particularly careful consideration regarding the appropriateness of a transfusion episode as well as the management of non-sanguinous fluid therapies should be employed in patients “at risk” for TACO as based on the highlighted risk factors. If transfusion is deemed unavoidable in such high risk patients, consideration of more intensive perioperative monitoring for signs respiratory distress may be justified. Finally, should the association between plasma therapies and TACO be confirmed in future clinical trials, the use of low-volume plasma alternatives such prothrombin complex concentrates may be warranted in at risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Overall Survival Curves from Date of Surgery for Cases and Controls

Postoperative survival Kaplan Meier Curve analyzed using stratified Cox proportional hazards regression taking into account the matched set study design. Median follow up for both groups was two years. *TACO = Transfusion associated circulatory overload

Table 1**Definitions for Transfusion-Associated Circulatory Overload****NHSN TACO Definition 2016**

New onset or exacerbation of 3 of the following within 6 hours of transfusion:

- Acute respiratory distress (dyspnea, orthopnea, cough)
- Evidence of positive fluid balance
- Elevated brain natriuretic peptide (BNP)
- Radiographic evidence of pulmonary edema
- Evidence of left heart failure
- Elevated central venous pressure (CVP)

ISBT TACO Definition 2011

Any 4 of the following occurring within 6 hours of completion of transfusion:

- Acute respiratory distress
- Tachycardia
- Elevated blood pressure
- Acute or worsening pulmonary edema of frontal chest radiograph
- Evidence of positive fluid balance

***An elevated BNP is supportive of TACO**

Adapted from Division of Healthcare Quality Promotion; Centers for Disease Control and Prevention. The National Healthcare Safety Network Manual: Biovigilance Component [Internet]. Atlanta, GA [2016 Jan] Available from: <http://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf> and

The Transfusion-associated circulatory overload Definition (2011 revision) by the International Society of Blood Transfusion Working Party on Haemovigilance in collaboration with The International Haemovigilance Network [Internet] Available from: <http://www.ihn-org.com/wp-content/uploads/2011/06/ISBT-definitions-for-non-infectious-transfusion-reactions.pdf>

NHSN = National Healthcare Safety Network, TACO = Transfusion-Associated Circulatory Overload, ISBT = International Society of Blood Transfusion

Table 2

Baseline Characteristics

Characteristic (all n (%) unless otherwise indicated)	TACO (N=163 [§])	Control (N=726 [§])	P-value*
Age (years) [‡]	71 (61 – 79)	71 (61 – 78)	[†]
Male Gender	91 (55.8)	411 (56.6)	[†]
Type of surgery			[†]
Abdominal	37 (22.7)	182 (25.1)	
OB/GYN	4 (2.5)	19 (2.6)	
Neurologic	3 (1.8)	13 (1.8)	
Orthopedic	20 (12.3)	94 (12.9)	
Spine	6 (3.7)	30 (4.1)	
Thoracic	10 (6.1)	39 (5.4)	
Transplant	17 (10.4)	76 (10.5)	
Urology	7 (4.3)	28 (3.9)	
Vascular	56 (34.4)	236 (32.5)	
Other	3 (1.8)	9 (1.2)	
Year of surgery			[†]
2004	112 (68.7)	490 (67.5)	
2011	51 (31.3)	236 (32.5)	
ASA physical status			0.002
I	1 (0.6)	6 (0.8)	
II	10 (6.1)	104 (14.3)	
III	108 (66.3)	497 (68.5)	
IV	40 (24.5)	114 (15.7)	
V	4 (2.5)	5 (0.7)	
Intraoperative Transfusion Volume (mL) [‡]	1154 (600 – 3649)	660 (350 – 1125)	<0.001
Positive Intraoperative Fluid Balance (mL) [‡]	5606 (3400 – 7806)	4128 (2942 – 5816)	<0.001
Blood Product Type			<0.001
Erythrocytes only	85 (52.1)	584 (80.4)	
FFP only	9 (5.5)	14 (1.9)	
Plts only	0 (0)	17 (2.3)	
Mixed Products	69 (42.3)	111 (15.3)	
Estimated Blood Volume (L) [‡]	4.9 (4.0 – 5.6)	4.9 (4.1 – 5.6)	0.363
Estimated Blood Loss (mL) [‡]	687 (156 – 1825)	500 (100 – 1000)	<0.001
Preoperative Hemoglobin (g/dL) [‡]	11.7 (9.7 – 13.2)	11.8 (10.1 – 13.3)	0.039

Characteristic (<i>all n (%) unless otherwise indicated</i>)	TACO (N=163 [§])	Control (N=726 [§])	P-value [*]
Body Mass Index (kg/m ²) [‡]	28.4 (24.4 – 32.8)	27.4 (24.0 – 31.5)	0.022
Emergency Surgery	53 (32.5)	101 (13.9)	<0.001
Duration of Surgery (mins)	272 (172 – 430)	261 (178 – 357)	0.001
Chronic Kidney Disease	36 (22.1)	104 (14.3)	0.020
Congestive Heart Failure	17 (10.4)	51 (7.0)	0.158
Echo evidence of LV dysfunction	39 (23.9)	100 (13.8)	0.002
Preoperative Beta blocker	108 (66.3)	390 (53.7)	0.002
Preoperative Diuretic	79 (48.5)	281 (38.7)	0.012
Preoperative Aspirin	84 (51.5)	400 (55.1)	0.408
Coronary Artery Disease	52 (31.9)	233 (32.1)	0.900
Moderate to Severe Liver Dx	11 (6.8)	32 (4.4)	0.072
History Alcohol Abuse	11 (6.8)	32 (5.2)	0.440

TACO = transfusion associated circulatory overload, OB/GYN = obstetrics and gynecology, ASA = American Society of Anesthesiologists, FFP = fresh frozen plasma, Plts = platelets, LV = left ventricular, Dx = disease

^{*} Each characteristic was assessed separately using conditional logistic regression taking into account the matched set study design

[‡] Cases and controls were matched on these variables

[‡] Median (interquartile range)

[§] BMI and estimated blood volume were missing for 10 (6%) TACO and 32 (4%) Controls, hemoglobin was missing for 12 (7%) TACO and 30 (4%) Controls, estimated blood loss was missing for 15 (9%) TACO and 59 (8%) controls, and duration of surgery was missing for 3 (2%) TACO and 9 (1%) controls.

Table 3

Multivariable analyses evaluating risk factors for TACO

	Volume Adjusted Analysis*		Multivariable Model	
Characteristic	OR (95% CI)	P-value	OR (95% CI)	P-value
Intraoperative Transfusion Volume (mL) [†]	–	–	1.0 (1.0 – 1.1)	0.273
Non-sanguineous Fluid Volume (mL) [†]	–	–	1.1 (1.1 – 1.1)	<0.001
Blood Product Type [‡]		<0.001		0.011
FFP only	6.2 (2.3 – 17.0)		6.2 (1.8 – 21.7)	
Plts only	N/A		N/A	
Mixed	3.4 (2.0 – 5.8)		1.9 (1.0 – 3.4)	
Estimated Blood Volume (mL) [†]	1.0 (0.8 – 1.3)	0.891	–	–
Estimated Blood Loss (mL) [†]	1.0 (0.9 – 1.1)	0.496	–	–
Preoperative Hemoglobin (g/dL) [§]	0.9 (0.8 – 1.0)	0.009	0.9 (0.8 – 1.0)	0.224
Body Mass Index (kg/m ²)	1.0 (1.0 – 1.1)	0.072	–	–
Emergency Surgery	4.6 (2.7 – 7.6)	<0.001	3.9 (2.1 – 7.2)	<0.001
Duration of Surgery	0.9 (0.8 – 1.0)	0.106	–	–
Chronic Kidney Disease	2.0 (1.2 – 3.2)	0.006	2.1 (1.2 – 3.7)	0.007
Congestive Heart Failure	1.8 (1.0 – 3.4)	0.057	–	–
Echo evidence of LV dysfunction	2.1 (1.3 – 3.3)	0.001	1.8 (1.1 – 3.1)	0.028
Preoperative Beta blocker	1.9 (1.3 – 2.9)	0.002	1.8 (1.1 – 2.9)	0.027
Preoperative Diuretic	1.5 (1.0 – 2.2)	0.030	1.4 (0.9 – 2.1)	0.173
Preoperative Aspirin	0.9 (0.6 – 1.4)	0.785	–	–
Coronary Artery Disease	1.2 (0.8 – 1.8)	0.497	–	–
Moderate to Severe Liver Dx	1.3 (0.5 – 3.6)	0.653	–	–
Alcohol Abuse	0.8 (0.4 – 1.7)	0.500	–	–

TACO = Transfusion Associated Circulatory Overload, OR = odds ratio, CI = confidence interval, FFP = fresh frozen plasma, Plts = platelets, LV = left ventricular, Dx = disease, N/A = not applicable

* each of the characteristics were assessed separately using conditional logistic regression with intraoperative transfusion volume and non-sanguineous fluid volume included as covariates

[†] Odds ratios are presented for a 500 ml increase

[‡] Compared to red blood cell transfusion only

δ per g/dL increase

$\parallel$ per kg/m² increase

∇ per 60 minute increase

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Table 4

Clinical Outcomes of Cases and Controls

Outcome	TACO (N=163)	Control (N=726)	P-value*
ICU LOS days, median (IQR)	(<i>n</i> = 161, 98.8%) 11.1 (4.3 – 30.5)	(<i>n</i> = 520, 71.6%) 6.5 (2.6 – 19.1)	<0.001
Hospital LOS days, median (IQR)	12 (7 – 22)	7 (5 – 10)	<0.001
Postoperative mechanical ventilation, n (%)	119 (73.0)	241 (33.2)	<0.001
Survival, % (95% CI)			<0.001
1 month	92.4 (88.4 – 96.6)	96.0 (94.6 – 97.5)	
3 months	84.9 (79.3 – 90.8)	93.5 (91.6 – 95.3)	
1 year	71.5 (64.5 – 79.4)	84.2 (81.5 – 87.0)	

ICU - intensive care unit, LOS - length of stay, IQR - interquartile range, TACO - transfusion associated circulatory overload

* ICU and Hospital LOS were compared between groups using quantile regression with matching variables and preoperative American Society of Anesthesiologists (ASA) physical status included as covariates. Postoperative mechanical ventilation was compared between groups using conditional logistic regression with preoperative ASA status included as a covariate. Survival estimates at 1 month, 3 months, and 1 year using the Kaplan-Meier method and overall survival was compared between groups using stratified Cox proportional hazards regression with preoperative ASA status included as a covariate.