Validation of a definition of excessive postoperative bleeding in infants undergoing cardiac surgery with cardiopulmonary bypass

Rachel S. Bercovitz, MD, MS,^{a,b,d} Allison C. Shewmake, MD,^c Debra K. Newman, PhD,^{d,e} Robert A. Niebler, MD,^{f,g} John P. Scott, MD,^{h,i} Eckehard Stuth, MD,^{g,h} Pippa M. Simpson, PhD,ⁱ Ke Yan, PhD,^j and Ronald K. Woods, MD, PhD^{g,k}

ABSTRACT

Objective: To derive and validate an objective definition of postoperative bleeding in neonates and infants undergoing cardiac surgery with cardiopulmonary bypass.

Methods: Using a retrospective cohort of 124 infants and neonates, we included published bleeding definitions and cumulative chest tube output over different postoperative periods (eg, 2, 12, or 24 hours after intensive care unit admission) in a classification and regression tree model to determine chest tube output volumes that were associated with red blood cell transfusions and surgical re-exploration for bleeding in the first 24 hours after intensive care unit admission. After the definition of excessive bleeding was determined, it was validated via a prospective cohort of 77 infants and neonates.

Results: Excessive bleeding was defined as ≥ 7 mL/kg/h for ≥ 2 consecutive hours in the first 12 postoperative hours and/or ≥ 84 mL/kg total for the first 24 postoperative hours and/or surgical re-exploration for bleeding or cardiac tamponade physiology in the first 24 postoperative hours. Excessive bleeding was associated with longer length of hospital stay, increased 30-day readmission rate, and increased transfusions in the postoperative period.

Conclusions: The proposed standard definition of excessive bleeding is based on readily obtained objective data and relates to important early clinical outcomes. Application and validation by other institutions will help determine the extent to which our specialty should consider this definition for both clinical investigation and quality improvement initiatives. (J Thorac Cardiovasc Surg 2018;155:2112-24)

Total transfusion volume is greater in bleeders (red) than nonbleeders (blue) in the first 7 days.

Central Message

We derived and validated a definition of postoperative bleeding that can be applied to neonatal and infant cardiac surgery patients in both the research and practice improvement settings.

Perspective

Excessive postoperative bleeding in neonates and infants undergoing surgical repair of congenital heart disease is a significant problem. Absence of a standardized objective definition of bleeding is a barrier to improving bleeding-related outcomes. The use of our definition has the potential to improve clinical research and patient care with respect to diagnosis, prevention, and treatment of bleeding.

See Editorial Commentary page 2125.

Excessive postoperative bleeding after surgical repair of congenital heart disease (CHD) requiring cardiopulmonary bypass (CPB) is associated with significant morbidity and

mortality.¹⁻⁴ However, there is no standard definition of postoperative bleeding that is universally applied in pediatric cardiac surgery patients. One consequence of

From the ^aMedical Sciences Institute and ^dBlood Research Institute, BloodCenter of Wisconsin, Milwaukee, Wis; ^bDivision of Hematology and Oncology, Departments of Pathology, Pediatrics, ^cSchool of Medicine, ^eDepartment of Pharmacology & Toxicology, ^fDivision of Pediatric Critical Care, Department of Pediatrics, ^gDivision of Pediatric Anesthesia, Department of Anesthesia, ^hDivision of Quantitative Health Sciences of Wisconsin, Department of Pediatrics, ⁱDepartment of Biostatistics, and ^jDivision of Pediatric Cardiothoracic Surgery, Department of Surgery, Medical College of Wisconsin, Milwaukee, Wis; and ^kHerman Heart Center, Children's Hospital of Wisconsin, Milwaukee, Wis.

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Address for reprints: Rachel S. Bercovitz, MD, MS, 225 E Chicago St, Box 30, Chicago, IL 60610 (E-mail: rbercovitz@luriechildrens.org). 0022-5223/\$36.00

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Abbreviations and Acronyms

CART	= classification and regression tree
CHD	= congenital heart disease
CI	= confidence interval
CICU	= cardiac intensive care unit
CPB	= cardiopulmonary bypass
CTO	= chest tube output
EBV	= estimated blood volume
RBC	= red blood cell

Scanning this QR code will take you to the supplemental figure, table, appendix, and video for this article.

having varying definitions of bleeding is a wide range of bleeding incidence (0%-42%) in studies of these patients.³⁻²⁰ As with other outcomes,²¹ intercenter variability in patient population and clinical practices likely contributes to a true difference in bleeding incidence; however, a study that uses chest tube output (CTO) greater than 20% of estimated blood volume (EBV) in 24 hours¹⁹ is likely to have more bleeders than a study that uses 20% EBV in the first 2 postoperative hours.¹¹

Frequently, postoperative bleeding is defined by using CTO, starting from the time of admission to the cardiac intensive care unit (CICU); many studies have a specific threshold above which is considered excessive (eg, ≥ 10 mL/kg in the first 4 postoperative hours),^{5-7,10,11,16,17,22} some report CTO as a continuous outcome,^{1,23,24} and others define bleeding as patients in the top 25th percentile for CTO.^{3,4,25} However, many of these definitions lack a rationale for the specific CTO threshold values that separate patients with and without bleeding. A validated definition of excessive postoperative bleeding that is associated with outcomes such as transfusions or surgical re-exploration could facilitate multi-institutional trials designed to address bleeding prevention and management in these complicated patients.

Children <12 months old comprise 56% of the patients who undergo surgical correction of CHD annually in the United States and account for 83% of the mortality.²⁶ Neonates and young infants are at the greatest risk of perioperative bleeding due to immature coagulation systems and exaggerated hemodilution due to the disproportionate ratio of CPB circuit volume to patient blood volume.^{27,28} A definition of bleeding for this specific group of patients that is objective and clinically relevant would be an asset to our specialty.

The goal of this study was to derive objective definitions of excessive postoperative CTO and bleeding in neonates and infants undergoing cardiac surgery with CPB. First, we reviewed the literature to identify appropriate articles on the subject of bleeding definitions specific to this patient population. Next, we applied these definitions as well as other iterations of cumulative CTO to a retrospective cohort to determine association with re-exploration for bleeding or transfusion of red blood cells (RBCs) in the first 24 hours after admission to the CICU, which are 2 of the most common sequelae of postoperative bleeding.² We then validated the derived definition in a prospective cohort of patients. Based on this analysis, we offer a new standardized definition of postoperative bleeding that may be appropriate for use in neonatal and infant pediatric cardiac surgery patients in both the research and practice improvement settings.

METHODS

Literature Review

To find definitions of bleeding used in studies of pediatric patients undergoing surgery with CPB, the following PubMed search was performed: (((((((bleed*) OR "excessive bleeding") OR "bled excessively") OR hemorrhage)) AND surgery) AND card*) AND "cardiopulmonary bypass." Search results were limited to articles in English in which the study population was children undergoing surgical repair of CHD with CPB. Articles were screened for relevance using title, and articles in which excessive postoperative bleeding was either a predictor variable or an outcome of interest were identified by review of the abstracts. Additional articles were found by manually searching the reference lists of primary articles and reviews. Only articles that provided a detailed definition of excessive bleeding in the methods section were selected for inclusion in this manuscript. Studies that compared median or mean CTO between 2 or more groups of patients were not included.

Determination and Validation of Bleeding Definition

All studies that used retrospective and prospective patient data were approved by the local institutional review board. IRB approval information: retrospective review, IRB of record: Children's Hospital of Wisconsin, approval date: June 18, 2014, IRB #: 14/88; prospective study (children ≤ 30 days old), IRB of record: Children's Hospital of Wisconsin, approval date: March 18, 2014, IRB #: 14/31; and prospective study (children ≥ 31 days old), IRB of record: Children's Hospital of Wisconsin, approval date: September 15, 2015, IRB #: 15/112.

Retrospective review (test cohort). A retrospective review of 130 neonates and infants <6 months old who underwent congenital heart surgery requiring CPB at Children's Hospital of Wisconsin from June 2012 to May 2014 was performed. Six patients were excluded because of placement on extracorporeal membrane oxygenation postoperatively. For subjects having more than 1 cardiac surgery during this time period, only the first operation was included.

Prospective studies (validation cohort). Two observational studies were performed of neonates and infants undergoing cardiac surgery at Children's Hospital of Wisconsin from June 2014 to May 2017. One study included neonates and the other included infants 31 to 365 days old at the time of surgery. A total of 76 subjects (44 neonates, 58%) were enrolled in these studies. Exclusion criteria were weight <2.5 kg and preoperative extracorporeal membrane oxygenation.

Standard Patient Management (Test and Validation Cohorts)

After induction of general anesthesia, patients were cannulated for CPB. The CPB circuit was primed with either whole blood (<5 days old) or equal amounts fresh RBCs and frozen plasma. Whole blood was preferred and used when available. Tranexamic acid was routinely administered (10–20 mg/kg) before incision. Most patients received both platelet and cryoprecipitate transfusions when transitioning off of the CPB circuit, although in cases in which patients had an on-CPB platelets >100,000/ μ L, the platelet transfusion was deferred based on the surgeon's preference. Further transfusions were administered as needed and at the discretion of the anesthesiologist and surgeon. Recalcitrant bleeding without a surgical source not responsive to blood product administration was treated with recombinant activated factor VII in dose increments of 90 μ g/kg. All efforts were made to achieve full hemostasis before transfer to the CICU.

Statistical Analysis

Data were summarized with medians and range. Univariate tests, including Wilcoxon rank sum tests, or Fisher exact test for categorical variables, were used to investigate relevant predictors of the outcomes of interest with a significance level of .05. For binary categorical variables, risk ratio is reported with 95% confidence intervals (CIs).

To determine a threshold of excessive CTO, the primary outcomes of interest were transfusion of RBCs or surgical re-exploration for bleeding in the first 24 CICU hours. Classification and regression trees (CART) were used to determine the amount (absolute and average, mL/kg) and duration (hours) of CTO that best predicted a positive outcome. Included in this CART analysis were all published definitions, cumulative CTO over different time spans (2, 4, 6, 12, and 24 hours postoperatively), and number of hours with CTO above various volumes (3, 4, 5, 6, 7, and 8 mL/kg/h).

CART analysis^{29,30} consists of 4 components: (1) an outcome variable (in this case, RBC transfusion or surgical re-exploration); (2) predictor variables (in this case, varying CTO amounts over varying time periods); (3) a test cohort (patients in the retrospective study); and (4) a validation cohort (patients in the prospective studies). An advantage of CART analysis over typical multiple variable regression models is that it can handle a large number of interrelated variables and goes through a series of yes/no questions to find important relationships (or nodes).³⁰ A stepwise approach of removing variables similar to nodes as they were established was used to achieve the *a priori* goal of having a definition that included thresholds for both early/acute high CTO volumes as well as sustained CTO over a clinically relevant time period. A complete list of variables as well as the CART analysis is in the [Appendix E1](#).

For time-to-discharge analysis, in-hospital mortality was treated as a competing outcome and separate analyses were performed on patients who underwent a Norwood procedure because some subjects remained hospitalized until the second stage surgery, which would have artificially prolonged length of stay. Probabilities of interest are the cumulative incidence functions for either event type, in-hospital mortality, or hospital discharge. These functions estimate the probability of experiencing a specific event by a given time while allowing for the possibility of other events to occur.³¹ To detect a 40% difference in incidence of the outcome of interest between patients with and without bleeding, assuming an incidence of bleeding >20%, we needed a minimum of 120 patients in the test cohort. Statistical analyses were performed with SAS Studio 3.5 (SAS, Cary, NC) and Prism 6.0h (GraphPad, La Jolla, Calif), and R (<https://r-project.org/>) was used for CART analysis.

RESULTS

Literature Review

Our original search yielded 593 articles, and an additional 15 articles were identified after a review of the references ([Figure E1](#)). Based on our selection criteria for

methodologic description of excessive bleeding, a total of 21 articles were included: 8 prospective studies, 11 retrospective studies, 1 review article, and 1 textbook chapter ([Table 1](#)).^{3–12,14–20,22,32–34} Three definitions were used by more than 1 study, resulting in 17 unique definitions.

Retrospective Review (Test Cohort)

Data from 124 infants $\leq$ 180 days old, including 68 (55%) neonates, undergoing cardiac surgical procedures requiring CPB were included in our final analysis. [Table 2](#) summarizes the demographic and clinical patient data.

Literature Review Results Applied to Test Cohort

Applying the published definitions to the retrospective cohort revealed that 90% (112) of these patients would have met the criteria for excessive bleeding based on 1 or more of these definitions. Of the 17 definitions, 1 was excluded from analysis because it defined bleeders as patients who had undergone re-exploration for bleeding but did not specify the criteria that prompted re-exploration.⁸ Of the 16 remaining definitions, 11 were associated with an increased risk of either RBC transfusion or re-exploration for bleeding in the first 24 postoperative hours (data not shown).

Determination of Excessive CTO

Although many of the published definitions were associated with a significantly greater risk of the outcomes of interest, none provided a rationale for the specific threshold chosen. Therefore, we included in the CART analysis not only the published definitions but also additional permutations of CTO in terms of volume, duration, and time period other than those presented in the published definitions. Thirty-nine patients (31.5%) had the outcomes of interest in the first postoperative 24 hours (26 patients received at least 1 RBC transfusion, 4 underwent re-exploration for bleeding, and 9 had both outcomes).

The first node of the CART analysis was CTO $\geq$ 84 mL/kg for 24 hours, risk ratio: 2.7 (95% CI, 1.7–4.3), $P = .0013$ ([Figure 1](#)). Because this number represented cumulative CTO, other variables of cumulative output were removed from the model for subsequent nodes (eg, 6- and 12-hour CTO). Of the measures that represented short-term, high CTO, none reached statistical significance as a second node in the model. However, CTO of $\geq$ 7 mL/kg/h for $\geq$ 2 consecutive hours in the first 12 hours was associated with the greatest risk ratio of RBC transfusion or re-exploration compared with similar variables (eg, $\geq$ 6 mL/kg/h for $\geq$ 2 hours or $\geq$ 5 mL/kg/h $\geq$ 3 hours), risk ratio: 2.3 (1.2–4.5) $P = .0640$. Patients who met one or both of the CTO criteria had a 2.8-fold greater risk of RBC transfusion or re-exploration than patients with less CTO (95% CI, 1.7–4.4), $P = .0002$. This increase in risk was slightly greater compared with the published definitions whose risk ratios ranged from 1.7 to 2.6.

TABLE 1. Articles identified through literature review

Study	Year	Type	Age	n	Definition	Incidence, %
Pekelharing and colleagues ¹⁴	2014	Prospective	<18 y	107	≥5 mL/kg/h in first 4 h	21.4
Moganasundram and colleagues ⁹	2010	Prospective	<5 y	50	>10 mL/kg in first 4 h	38
Faraoni and colleagues ³²	2015	Retrospective	≤16 y	150	>10% EBV in first 6 h	23
Savan and colleagues ²⁰	2014	Retrospective	≤16 y	182	>10% EBV in first 6 h	28.9
Timpa and colleagues ¹⁸	2016	Prospective	<18 y	161	>10 mL/kg in the first CICU hour	26
Niebler and colleagues ¹⁰	2012	Prospective	<18 y	60	> 6 mL/kg/h for ≥2 consecutive hours in 6 h	31.7
Niles and colleagues ¹²	2008	Retrospective	<18 y	328	> 4 mL/kg/h for ≥2 consecutive hours in 7 h	NA
Tobias and colleagues ²²	2004	Retrospective	<18 y	17	≥12 mL/kg for the first 3 postoperative hours	NA
Razon and colleagues ¹⁶	2005	Prospective	≤19 y	5	>8 mL/kg for any 1 h or >4 mL/kg/h for ≥3 consecutive hours	NA
Agarwal and colleagues ⁵	2015	Retrospective	<18 y	253	>10 mL/kg in the first hour or >5 mL/kg for 3 consecutive hours in 12 h	42
Guay and Rivard ³³	1996	Review	NA	NA	>10% EBV in any 1 hour or >5% EBV for 3 consecutive hours in 24 hours	NA
Oliver ³⁴	2005	Textbook	<18 y	NA	>10% EBV in any 1 hour or >5% EBV for 3 consecutive hours in 24 hours	NA
Singh and colleagues ¹⁷	2012	Retrospective	<15 y	20	>10% EBV in any 1 hour or >5% EBV for 3 consecutive hours in 24 hours	NA
Tirosh-Wagner and colleagues ¹⁹	2011	Prospective	≤10 y	15	>20% EBV in 24 h	NA
Hoda and colleagues ⁷	2016	Retrospective	<18 y	82	>4 mL/kg/h average for 24 h	0
Pychynska-Pokorska and colleagues ¹⁵	2004	Prospective	<5 y	8	Children ≤5 kg: ≥10 mL/kg/h Children ≥5 kg: ≥2 mL/kg/h	NA
Williams and colleagues ¹¹	1999	Prospective	<18 y	494	≥20% EBV in hours 0-2 or ≥20% EBV in hours 2-6 or ≥30% EBV in hours 7-12	19
Brenner and colleagues ⁶	2015	Retrospective	<18 y	91	≥20% EBV in hours 0-2 or ≥20% EBV in hours 2-6 or ≥30% EBV in hours 7-12	28.5
Guzzetta and colleagues ³	2015	Retrospective	≤30 d	167	Top 25th percentile for CTO in 24 h	25
Wolf and colleagues ⁴	2014	Retrospective	<1 y	1071	Top 25th percentile for CTO in 12 h	25
Kylasam and colleagues ⁸	2009	Retrospective	≤90 mo	25	Required re-exploration for bleeding	2.5

EBV, Estimated blood volume (<10 kg, 85 mL/kg; 10-20 kg, 80 mL/kg; 20-30 kg, 7 mL/kg; and 30-40 kg, 70 mL/kg^{17,35}); CICU, cardiac intensive care unit; NA, not available; CTO, chest tube output.

Bleeding Definition

Based on this analysis, we define excessive CTO as ≥84 mL/kg total for the first 24 postoperative hours (≥3.5 mL/kg/h average) and/or ≥7 mL/kg/h for ≥2 consecutive hours in the first 12 postoperative hours. In addition, to account for patients who may undergo re-exploration for bleeding before meeting the excessive CTO criteria or develop cardiac tamponade physiology secondary to bleeding rather than have excessive CTO, we propose a definition for excessive bleeding as patients who meet 1 or more of the following criteria:

- (1) CTO ≥ 7 mL/kg/h for ≥2 consecutive hours in the first 12 postoperative hours;
- (2) ≥84 mL/kg total for the first 24 postoperative hours; or

- (3) re-exploration for bleeding or cardiac tamponade physiology in the first 24 postoperative hours.

Thirty-one patients (25%) met criteria for excessive postoperative bleeding (18 patients had excessive CTO, 1 was re-explored for bleeding, 5 were re-explored for tamponade in the first 24 postoperative hours, and 7 had both excessive CTO and were re-explored for bleeding). In univariate analyses, patients with excessive bleeding were younger, weighed less, spent more time on CPB, and had a lower minimum body temperature intraoperatively (Table 3).

Prospective Study (Validation Cohort)

The 76 neonates and infants in the validation cohort were similar to those in the test cohort, as Table 2 shows. Of the

TABLE 2. Patient demographics and clinical characteristics in the test (retrospective) cohort versus the validation (prospective) cohort

Demographics, n = 200	Median (range) or n (%)	Test cohort n = 124 (%)	Validation cohort n = 76 (%)	P value
Weight, kg	3.8 (2.2-13.3)	3.8 (2.2-8.7)	3.8 (2.6-13.3)	.3388
Age, d	13.5 (0-306)	16 (0-180)	10 (1-306)	.9619
Sex, female	97 (48.5)	56 (45.2)	41 (54)	.2461
STAT score				
1	24 (12)	15 (12.1)	9 (11.8)	.1979
2	42 (21)	22 (17.7)	20 (26.3)	
3	32 (16)	20 (16.1)	12 (15.8)	
4	54 (27)	39 (31.5)	15 (19.7)	
5	44 (22)	24 (19.4)	20 (26.3)	
NA	4 (2)	4 (3.2)	0	
Preoperative labs				
Hematocrit, %	41.2 (24.2-60.5)	41.3 (24.2-55.7)	40.8 (31.4-60.5)	.8621
Platelet count, $\times 10^3/\mu\text{L}$	328 (56-755)	349 (104-755)	317 (56-595)	.0246
MPV, fL	7.6 (5.4-16.8)	7.8 (5.6-11.2)	7.4 (5.4-6.8)	.1877
High MPV, ≥ 9.5 fL	23 (11.5)	25 (12.1)	8 (10.5)	.8221
Surgeon*				
1	50 (25)	31 (25)	19 (25)	ND
2	62 (31)	51 (41.1)	11 (15.5)	
3	77 (38.5)	42 (33.9)	35 (46.1)	
4	11 (5.5)	0	11 (14.5)	
Time on CPB, min	161 (31-696)	161 (31-354)	163 (40-696)	.6268
Minimum temperature, °C	28 (14.1-37)	28 (16.7-37)	29.7 (14.1-35)	.0881
DHCA, yes	73 (36.5)	47 (37.9)	26 (34.2)	.6513
Intraoperative rFVIIa	14 (7)	11 (8.9)	3 (4)	.2569
Prime				
Whole blood	99 (49.5)	72 (58.1)	27 (35.5)	.0036
RBCs + plasma	98 (49)	50 (40.3)	48 (63.2)	
Other	3 (1.5)	2 (1.6)	1 (1.3)	
Delayed chest closure	95 (47.5)	63 (50.8)	32 (42.1)	.2464
Genetic syndrome				
No	150 (75)	100 (80.7)	50 (65.8)	.0483
Trisomy 21	23 (11.5)	13 (10.5)	10 (13.2)	
22q11 deletion syndrome	10 (5)	4 (3.2)	6 (7.9)	
16p duplication	3 (1.5)	0	3 (4)	
Other	14 (7)	7 (5.7)	7 (9.2)	
Single-ventricle physiology	86 (43)	54 (43.6)	32 (42.1)	.8837
Cyanotic heart disease (pre)	152 (76)	88 (71)	64 (84.2)	.0406
Procedure				
ASD creation	2 (1)	1 (0.8)	1 (1.3)	
ASD or VSD repair	20 (10)	13 (10.5)	7 (9.2)	
AVC repair	15 (7.5)	10 (8.1)	5 (6.6)	
Truncus arteriosus repair	4 (2)	3 (2.4)	1 (1.3)	
TAPVC/R repair	6 (3)	4 (3.2)	2 (2.6)	
TOF repair	21 (11.5)	9 (7.2)	12 (15.8)	
Pulmonary atresia repair	4 (2)	4 (3.2)	0	
Norwood procedure	43 (21.5)	23 (18.6)	20 (26.3)	
Heart transplant	5 (2.5)	5 (4)	0	
Arterial switch operation	25 (12.5)	17 (13.7)	8 (10.5)	
DORV repair	3 (1.5)	2 (1.6)	1 (1.3)	

(Continued)

TABLE 2. Continued

Demographics, n = 200	Median (range) or n (%)	Test cohort n = 124 (%)	Validation cohort n = 76 (%)	P value
Aortic arch repair	5 (2.5)	5 (4)	0	
Interrupted aortic arch repair	9 (4.5)	6 (4.8)	3 (4)	
Systemic to pulmonary shunt	7 (3.5)	5 (4)	2 (2.6)	
Bidirectional Glenn	11 (5.5)	8 (6.5)	3 (4)	
Hemi-Fontan	5 (2.5)	1 (0.8)	4 (5.3)	
Valve repair/replacement	7 (3.5)	3 (2.4)	4 (5.3)	
Other	8 (4)	5 (4)	3 (4)	

Data are expressed in either n (%) (Fisher exact test) or median (range) (Wilcoxon rank some test). *STAT*, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; *NA*, not available; *MPV*, mean platelet volume (normal range = 6.5–9 fL); *ND*, not determined; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest (<22°C); *rFVIIa*, recombinant activated factor VII; *RBCs*, red blood cells; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *AVC*, atrioventricular canal defect; *TAPVC/R*, total anomalous pulmonary venous connection/return; *TOF*, tetralogy of Fallot; *DORV*, double-outlet right ventricle. *Statistical analysis not performed for surgeon due to changes in staffing during the studies. Study populations were similar, although the validation cohort had more patients with a genetic syndrome and a greater percentage with cyanotic heart disease. The difference in baseline platelet count is statistically, but not clinically, significant.

76 neonates and infants in the prospective study, 15 (19.5%) met the criteria for excessive CTO, and those had a 2.2-fold increase in risk of either RBC transfusion or re-exploration (95% CI, 1.5–3.2, $P = .0012$) compared with the 61 patients without excessive CTO. Four additional patients underwent re-exploration for cardiac tamponade for a total of 19 patients (24.7%) who met criteria for postoperative bleeding. Risk ratio of RBC transfusion in patients with excessive bleeding was 2.4 (95% CI, 1.6–3.6, $P = .0004$). Variables associated with increased bleeding

risk were similar in both the test and validation cohorts (Tables 3 and 4).

Outcomes in Test and Validation Cohorts

The validation and test cohorts were combined to evaluate outcomes in patients with and without excessive bleeding. In addition to being more likely to receive a RBC transfusion in the first 24 hours, patients with excessive bleeding who underwent transfusion received a greater volume of RBCs (25.6 mL/kg vs 14.4 mL/kg, $P = .0002$) (Table 5). Excessive bleeding in the first 24 postoperative hours was also associated with increased number of transfusions of all blood components in the first postoperative week (Table 5).

In patients not undergoing a Norwood procedure, those with excessive bleeding had a longer length of hospital stay but a shorter time to in-hospital mortality than patients without bleeding (Figure 2). Among all patients, there was a trend toward increased risk of in-hospital mortality, 3.3% in patients without bleeding and 10% in patients with bleeding; however, this was not statistically significant ($P = .1250$, Table 5). Patients with excessive bleeding had an increased risk of unplanned readmission ≤30 days after discharge and thrombus within 14 days of surgery (Table 5).

DISCUSSION

The lack of a standardized, objective definition of excessive postoperative bleeding in neonates and infants undergoing cardiac surgery is a barrier to improving bleeding-related outcomes in these patients. The International Initiative for Haemostasis Management in Cardiac Surgery proposed and validated a universal definition of perioperative bleeding for adults undergoing cardiac surgery with CPB.³⁶ This scale uses a combination of CTO, transfusions and factor replacement received, and surgical re-exploration. For neonates and infants, the use of a similar rubric as the universal definition of perioperative bleeding may be valuable, but simply scaling CTO output linearly based on weight with respect to the adult data is not useful, eg, >2000 mL in 12 hours is

FIGURE 1. Summary of CART analysis of CTO as a predictor of the combined outcome of RBC transfusion and/or re-exploration for bleeding or tamponade in the first 24 postoperative hours in the test cohort. The primary node was an average CTO of 84 mL/kg for the first 24 postoperative hours, and the secondary node was ≥2 consecutive hours with ≥7 mL/kg/h in the first 12 postoperative hours. The Appendix E1 contains the full list of variables inputted into the model for both the first and second nodes. CTO, Chest tube output; PO, postoperative.

TABLE 3. Patient demographics and clinical characteristics of the retrospective (test) cohort, comparing patients with and without excessive bleeding

Demographics n = 124	Patients without bleeding (n = 93)	Patients with bleeding (n = 31)	Risk ratio	P value
Weight, kg	4.2 (2.4-8.7)	3.1 (2.2-7.5)		<.0001
Age, d	49 (0-180)	8 (0-146)		.0002
Sex, female	39 (42)	17 (54.8)	1.3 (0.8-2)	.2202
STAT score				
1	13 (14.0)	2 (6.4)		.0117
2	20 (21.5)	2 (6.4)		
3	15 (16.1)	5 (16.1)		
4	31 (33.3)	8 (25.8)		
5	11 (11.8)	13 (41.9)		
NA	3 (3.2)	1 (3.2)		
Preoperative labs				
Hematocrit, %	41.2 (24.2-55.7)	41.8 (26.2-52.9)		.9733
Platelet count, $\times 10^3/\mu\text{L}$	370 (104-755)	314 (108-609)		.1150
MPV, fL	7.6 (5.6-11.2)	8.0 (6-11.2)		.0403
High MPV, ≥ 9.5 fL	7 (7.5)	7 (23.3)	3.4 (1.3-8.7)	.0116
Surgeon				
1	27 (29.0)	4 (12.9)		.0758
2	33 (35.5)	18 (58.1)		
3	33 (35.5)	9 (29.0)		
Time on CPB, min	156 (31-354)	182 (78-287)		.0530
Minimum temperature, °C	28.0 (17.0-37.0)	18 (16.7-32)		.0024
DHCA, yes	28 (30.1)	19 (61.3)	2 (1.3-3.1)	.0027
Intraoperative FVIIa	5 (5.4)	6 (19.4)	3.6 (1.1-11)	.0278
Prime				
Whole blood	61 (65.6)	11 (35.5)		.0068
RBCs + plasma	31 (33.3)	19 (61.3)		
Other	1 (1.1)	1 (3.2)		
Delayed chest closure	37 (39.8)	26 (83.9)	2.1 (1.5-2.9)	<.0001
Genetic syndrome				
No	73 (78.4)	27 (87.2)		.2325
Trisomy 21	12 (12.9)	1 (3.2)		
22q11 deletion syndrome	2 (2.2)	2 (6.4)		
16p duplication	0	0		
Other	6 (6.5)	1 (3.2)		
Single-ventricle physiology	34 (36.6)	20 (64.5)	1.8 (1.2-2.6)	.0113
Cyanotic heart disease (pre)	61 (65.6)	27 (87.1)	1.3 (1.1-1.7)	.0234
Procedure				
ASD creation	0	1 (3.2)		
ASD or VSD repair	11 (11.8)	2 (6.5)		
AVC repair	10 (10.8)	0		
Truncus arteriosus repair	2 (2.2)	1 (3.2)		
TAPVC/R repair	3 (3.2)	1 (3.2)		
TOF repair	8 (3.2)	1 (3.2)		
Pulmonary atresia repair	2 (2.2)	2 (6.5)		
Norwood procedure	11 (11.8)	12 (38.7)		
Heart transplant	4 (4.3)	1 (3.2)		
Arterial switch operation	12 (12.9)	5 (16.3)		
DORV repair	2 (2.2)	0		
Aortic arch repair	4 (4.3)	1 (3.2)		

(Continued)

TABLE 3. Continued

Demographics n = 124	Patients without bleeding (n = 93)	Patients with bleeding (n = 31)	Risk ratio	P value
Interrupted aortic arch repair	4 (4.3)	2 (6.5)		
Systemic to pulmonary shunt	4 (4.3)	1 (3.2)		
Bidirectional Glenn	8 (8.6)	0		
Hemi-Fontan	1 (1.1)	0		
Valve repair/replacement	3 (3.2)	0		
Other	4 (4.3)	1 (3.2)		

Patients with and without bleeding had significant differences and in general patients with bleeding were younger, weighed less, and were more likely to have DHCA, delayed chest closure, and have cyanotic heart defects. Many of these variables are interdependent (eg, patients with single-ventricle physiology tend to be younger, require longer surgery with lower minimum body temperature, etc), and there was uneven distribution of neonates amongst the surgeons. *STAT*, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; *NA*, not available; *MPV*, mean platelet volume (normal range = 6.5–9 fL); *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest (<22°C); *FVIIa*, recombinant activated factor VII; *RBCs*, red blood cells; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *AVC*, atrioventricular canal defect; *TAPVC/R*, total anomalous pulmonary venous connection/return; *TOF*, tetralogy of Fallot; *DORV*, double-outlet right ventricle.

an average of 2.2 mL/kg/h in a 75-kg adult; in our study, 86 of the 200 infants (43%), and in particular 57% of neonates, in both our test and validation cohorts would have had Grade 5 bleeding based on such scaling.

Despite the lack of consensus on a bleeding definition for neonates and infants, there are many reports of patients with excessive bleeding having inferior outcomes and longer lengths of hospital stay.^{3,4,13} These inferior outcomes may be directly associated with bleeding or secondary to the treatments required to manage bleeding such as transfusions or additional surgery.² CTO is frequently used to determine postoperative bleeding. Advantages of using CTO include that it is easily quantifiable and begins at the set time of admission to CICU. In addition, it is routinely collected for clinical care and therefore should be readily available for use in both retrospective and prospective studies. However, determining the quantity of CTO that is excessive can be difficult, as evidenced by the various definitions in the literature.^{3,5,7,9–11,36}

A challenge to defining bleeding is that there is no gold standard to which different levels of CTO can be compared. However, we propose that a definition of excessive CTO should be one that relates directly to risk of additional clinically relevant interventions. RBC transfusion and/or surgical re-exploration for bleeding, which expose patients to risks such as infection or anesthesia, were chosen because they are direct consequences for excessive CTO.² Re-exploration for bleeding or cardiac tamponade physiology without excessive CTO was included in our final definition of bleeding because patients may be taken for re-exploration for a bleeding-related event without having increased CTO. This definition is as follows:

1. CTO ≥7 mL/kg/h for ≥2 consecutive hours in the first 12 postoperative hours and/or;
2. ≥84 mL/kg for the first 24 postoperative hours and/or; and
3. re-exploration for bleeding or tamponade in the first 24 postoperative hours.

Predictors of excessive bleeding based on this definition are similar to published ones: weight and minimum intraoperative temperature.^{1,11} Of interest and likely importance, we found that having a preoperative mean platelet volume greater than our institution’s normal range (6.0–9.5 fL) was also associated with excessive bleeding in both the test and validation cohorts. Because platelet dysfunction is thought to be a primary contributor to perioperative bleeding, the relationships between platelet size, genetic syndromes such as 22q11 deletion syndrome, on-CPB platelet count and function, and postoperative outcomes such as bleeding and transfusion requirements is an area for further investigation. In the retrospective cohort, prime with whole blood was associated with reduced bleeding risk. Gruenwald and colleagues found that whole blood prime was associated with decreased CTO postoperatively, and our retrospective data support this finding whereas our prospective data do not.³⁷

Our definition of bleeding is associated with worse outcomes, similar to other published reports.^{3,4} Among patients not undergoing a Norwood procedure, patients with postoperative bleeding had a longer length of stay and a shorter time to in-hospital death than patients without excessive bleeding. Patients with excessive bleeding who received more RBC, plasma, and platelet transfusions in the first postoperative week were more likely to develop a clinically significant thrombus in the first 2 postoperative weeks and were more likely to be readmitted within 30 days of primary discharge.

The decisions to transfuse RBCs or surgically re-explore a patient are difficult to standardize; however, the limited time course of this study and the relative limited number of clinicians involved in our clinical care team who typically jointly made these decisions reduces the impact of interprovider variability. CTO is a serosanguinous fluid, and depending on a patient’s individual situation, may be more or less reflective of blood loss versus fluid loss, which is why we chose RBC transfusion rather than plasma

TABLE 4. Patient demographics and clinical characteristics of the prospective (validation) cohort, comparing patients with and without excessive bleeding

Demographics n = 76	Patients without bleeding (n = 57)	Patients with bleeding (n = 19)	Risk ratio	P value
Weight, kg	4.4 (2.6-13.3)	3.0 (2.6-6.7)		.0013
Age, d	77 (1-306)	7 (1-192)		.0024
Sex, female	29 (50.9)	12 (63.1)	1.2 (0.8-2)	.4304
STAT score				
1	9 (15.8)	0		.0003
2	18 (31.6)	2 (10.5)		
3	3 (21)	0		
4	7 (12.3)	8 (42.1)		
5	11 (19.3)	9 (47.4)		
Preoperative labs				
Hematocrit, %	40.7 (31.4-60.5)	43.2 (32.2-58.4)		.1991
Platelet count, $\times 10^3/\mu\text{L}$	326 (128-595)	259 (56-474)		.0331
MPV, fL	7.2 (5.4-10.1)	8.4 (6.1-16.8)		.0052
High MPV, ≥ 9.5 fL	1 (1.8)	7 (36.8)	21 (2.7-159.9)	.0002
Surgeon*				ND
1	13 (22.8)	6 (31.6)		
2	5 (8.8)	6 (31.6)		
3	29 (50.9)	6 (31.6)		
4	10 (17.5)	1 (5.2)		
Time on CPB, min	149 (40-373)	202 (88-696)		.0414
Minimum temperature, °C	30.3 (14.1-35)	17.3 (15.1-33.6)		.0003
DHCA, yes	12 (21.1)	14 (73.7)	3.5 (1.9-6.2)	<.0001
Intraoperative FVIIa	2 (3.5)	1 (5.3)	1.5 (0.1-15.7)	1.0
Prime				
Whole blood	20 (35)	7 (36.8)		1.0000
RBCs + plasma	36 (63.2)	12 (63.2)		
Other	1 (1.8)	0		
Delayed chest closure	17 (29.8)	15 (79)	2.6 (1.6-4.2)	.0003
Genetic syndrome				
No	38 (66.7)	12 (63.2)		.6051
Trisomy 21	8 (14)	2 (10.5)		
22q11 deletion syndrome	3 (5.3)	3 (15.8)		
16p duplication	3 (5.3)	0		
Other	5 (8.7)	2 (10.5)		
Single-ventricle physiology	18 (31.6)	14 (73.7)	2.3 (1.4-3.8)	.0025
Cyanotic heart disease (pre)	45 (79)	19 (100)	1.3 (1.1-1.7)	.0307
Procedure				
ASD creation	1 (1.8)	0		
ASD or VSD repair	7 (12.3)	0		
AVC repair	5 (8.8)	0		
Truncus arteriosus repair	0	1 (5.3)		
TAPVC/R repair	1 (1.8)	1 (5.3)		
TOF repair	9 (15.8)	3 (15.8)		
Pulmonary atresia repair	0	0		
Norwood procedure	11 (19.3)	9 (47.4)		
Heart transplant	0	0		
Arterial switch operation	8 (14)	0		
DORV repair	0	1 (5.3)		
Aortic arch repair	0	0		

(Continued)

TABLE 4. Continued

Demographics n = 76	Patients without bleeding (n = 57)	Patients with bleeding (n = 19)	Risk ratio	P value
Interrupted aortic arch repair	1 (1.8)	2 (10.6)		
Systemic to pulmonary shunt	1 (1.8)	1 (5.3)		
Bidirectional Glenn	3 (5.3)	0		
Hemi-Fontan	3 (5.3)	1 (5.3)		
Valve repair/replacement	4 (7)	0		
Other	3 (5.3)	0		

Differences between patients with and without excessive postoperative bleeding are similar in the validation cohort as the test cohort. *STAT*, Society of Thoracic Surgeons–European Association for Cardio-Thoracic Surgery; *MPV*, mean platelet volume (normal range = 6.5–9 fL); *ND*, not determined; *CPB*, cardiopulmonary bypass; *DHCA*, deep hypothermic circulatory arrest (<22°C); *FVIIa*, recombinant activated factor VII; *RBCs*, red blood cells; *ASD*, atrial septal defect; *VSD*, ventricular septal defect; *AVC*, atrioventricular canal defect; *TAPVC/R*, total anomalous pulmonary venous connection/return; *TOF*, tetralogy of Fallot; *DORV*, double-outlet right ventricle. *Statistical analysis not performed for surgeon due to changes in staffing during the studies.

transfusion as an indicator of blood loss. In addition, CTO in the first few hours after surgery is more commonly reflective of blood loss.

The proposed definition was developed and validated only in neonates and infants, collectively representing the majority of greater risk patients with a greater percentage of postoperative complications. For this group, our definition may be superior to previously published definitions that were based on cohorts with broader age ranges (Video 1). However, the methodology used to determine the amount and duration of CTO associated with outcomes of interest could theoretically be applied to older pediatric patients. The purpose of our standardized definition of postoperative excessive bleeding is for use as a common data element in both single- and multi-institutional trials, as well as research databases and to facilitate the

development of predictive models to identify at-risk patients as well as optimize interventions to prevent and treat postoperative bleeding.

Limitations

Because the management of bleeding and transfusion practice varies widely across pediatric cardiac centers, our single-institution study and the resultant definition of bleeding would likely lead to variations in incidence of bleeding and other secondary outcomes (length of stay, duration of mechanical ventilation, mortality, etc); external validation is needed to verify the utility of this definition. This concern does not negate the value of this definition based on clinically relevant and measurable criteria. We acknowledge the somewhat-arbitrary nature of outcome criteria on which to base the CTO analysis (eg, transfusion and/or

TABLE 5. Postoperative transfusions and complications in patients with and without excessive postoperative bleeding in the retrospective cohort

Outcome	All subjects n = 200 (%)	Patients without bleeding n = 150 (%)	Patients with bleeding n = 50 (%)	Risk ratio (95% CI)	P value
RBCs/WB transfused in the first 24 h postoperatively					
Number	63 (31.5)	32 (20.7)	31 (64)	3.1 (2.1–4.6)	<.0001
Volume, mL/kg*	16 (1.2–227.7)	14.4 (1.2–30.7)	25.6 (6.7–227.7)		.0002
Transfused in the first 7 d postoperatively, n (%)					
RBCs/WB	93 (46.5)	53 (35.5)	40 (80)	2.3 (1.7–3)	<.0001
Plasma	65 (32.5)	25 (16.7)	40 (80)	2.3 (1.7–3)	<.0001
Platelets	22 (11)	11 (7.3)	11 (22)	3.0 (1.3–6.5)	.0077
Transfused in the first 7 d, mL/kg*					
RBCs/WB	16.1 (1.2–581)	14.9 (1.2–128.7)	32.4 (9.8–581)		<.0001
Plasma	26.2 (4.5–479)	20.8 (8.9–130.9)	37.1 (4.5–479)		.0217
Platelets	19.3 (1.8–138)	15.7 (1.8–44.1)	37.5 (2.4–138)		.1300
Donor exposures	5 (0–40)	4 (0–22)	8.5 (1–40)		.0002
Infection	24 (12)	19 (12.7)	5 (10)	0.8 (0.3–2.1)	.8026
Stroke†	5 (2.5)	4 (2.8)	1 (2)	0.8 (0.1–6.7)	1.0
Thrombotic event	18 (9)	9 (6)	9 (18)	3.0 (1.2–7.1)	.0194
Unplanned readmission ≤30 d‡	29 (14.5)	15 (10.3)	14 (31.1)	3.0 (1.5–5.8)	.0016
In-hospital mortality	10 (5)	5 (3.3)	5 (10)	3.0 (0.9–10)	.1250

CI, Confidence interval; RBC, red blood cell; WB, whole blood. *Analysis includes only transfused patients. †Missing data for 9 patients (6 without and 3 with excessive bleeding).

‡Excludes the 10 patients who died before discharge.

FIGURE 2. Time to discharge or in-hospital death in patients with (red line) and without (blue line) excessive bleeding undergoing either a Norwood procedure (A) or another surgery (B). Patients were divided based on operation because patients undergoing a Norwood procedure were likely to remain hospitalized until the second stage surgery, whereas other patients were not. There was no difference in LOS or time to in-hospital mortality based on bleeding in patients undergoing a Norwood procedure, whereas patients with excessive bleeding who did not undergo a Norwood procedure had a significantly longer LOS (median = 25 days vs 14 days, $P = .05$) and a shorter time to mortality ($P = .044$) than patients without bleeding. Please see [Table E1](#) for the 95% confidence interval on days 15, 30, 60, and 90. NB, No bleeding; DC, discharged; B, bleeding; IHD, in-hospital death.

re-exploration). However, we suggest that most clinicians would agree that these are clinically relevant outcomes directly related to bleeding. One may question the use of re-exploration for cardiac tamponade physiology, as such

an event could occur in the absence of large volume blood loss (eg, focal tamponade from excessive clotting). However, in our experience, this is an exception. Because re-exploration relating to a bleeding process indeed seems

Validation of a definition of excessive postoperative bleeding in infants undergoing cardiac surgery with cardiopulmonary bypass

Rachel S. Bercovitz, MD MS

Associate Medical Director, BloodCenter of Wisconsin
Assistant Professor of Pediatrics and Pathology,
Medical College of Wisconsin

VIDEO 1. Dr Rachel Bercovitz summarizes the study's objectives and findings. Video available at: [http://www.jtcvsonline.org/article/S0022-5223\(17\)32846-5/fulltext](http://www.jtcvsonline.org/article/S0022-5223(17)32846-5/fulltext).

relevant, we felt it was necessary to include it in the definition.

CONCLUSIONS

CTO is commonly used to define postoperative bleeding, but published definitions vary widely and may not correlate with poor outcomes. The definition of excessive bleeding proposed in this manuscript is associated with relevant outcomes such as increased transfusions and re-exploration, and preliminary investigation suggests that excessive bleeding is associated with worse postoperative outcomes such as longer length of stay or increased risk of unplanned readmission. A standard definition, like the one proposed, will improve strategies to study, diagnose, prevent, and treat excessive postoperative bleeding in neonates and infants undergoing cardiac surgery with CPB.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: congenital heart disease, blood loss, postoperative, cardiopulmonary bypass, infants, cardiac surgery, blood transfusions

APPENDIX E1

Variables inputted into the CART model:
CTO as a continuous variable:

Average for the first 2, 4, 6,* 12,* and 24* hours†
CTO in hours 1-2, 3-6,* and hours 7-12* postoperatively

Published definitions:

Agarwal and colleagues⁵
Faraoni and colleagues³²
Guay and Rivard³³
Guzzetta and colleagues³
Hoda and colleagues^{7,*}
Moganasundram and colleagues⁹
Niebler and collegas¹⁰
Niles and colleagues¹²
Pychynska-Pokorska and colleagues¹⁵
Pekelharing and colleagues¹⁴
Razon and colleagues¹⁶
Timpa and colleagues¹⁸
Tirosh-Wagner and colleagues¹⁹
Tobias and colleagues²²

Williams and colleagues¹¹
Wolf and colleagues⁴

CTO in a single hour (mL/kg/h) in the first 6 and 12 hours:
≥10, ≥15, ≥20
CTO in ≥2 nonconsecutive hours (mL/kg/h) in the first 6
and 12 hours: ≥10, ≥15, ≥20
CTO per hour for consecutive or no-consecutive hours
during different postoperative time periods (all permuta-
tions listed below were included):

CTO, mL/kg/h	Number of hours	Time period (from time of CICU admission)
3	2	6
4	3	12
5	4	24
6	5	
7	6	
8		
9		

CTO, Chest tube output; CICU, cardiac intensive care unit.

* Variables not included in the second node.
† All hour values refer to hour 0 being time of admission to the CICU. As anticipated, very high values (eg, ≥20 mL/kg for ≥2 hours in the first 6 hours) had excellent specificity but poor sensitivity. Relatively low values (eg, ≥2 mL/kg/h average for the first 24 hours) had good sensitivity but poor specificity.

FIGURE E1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. Search terms in PubMed were (((((((bleed*) OR “excessive bleeding”) OR “bled excessively”) OR HEMORRHAGE)) AND surgery) AND card*) AND “cardiopulmonary bypass.” Additional sources were found by looking through references of full-text articles that were assessed for eligibility. Search updated February 17, 2017.

TABLE E1. Estimated probability with confidence intervals time-to-event analyses in Figure 2, A and B

	Day 15	Day 30	Day 60	Day 90
Norwood Patients				
Hospital discharge ($P = .5000$)				
Bleeding	0 (0-10.3)	4.8 (0-18.2)	47.6 (34.4-60.8)	71.4 (59.6-83.2)
No bleeding	4.5 (0-12.6)	18.2 (10.8-25.5)	63.6 (58.1-69.2)	72.7 (67.8-77.6)
In-hospital death ($P = .6300$)				
Bleeding	0 (0-3.9)	0 (0-5.5)	4.8 (0-11.4)	4.8 (0-12.5)
No bleeding	0 (0-0)	4.5 (3.2-5.9)	4.5 (2.3-6.8)	4.5 (2.3-6.8)
Non-Norwood Patients				
Hospital discharge ($P = .0500$)				
Bleeding	27.6 (17.3-37.9)	58.6 (45.2-72.1)	82.8 (69.6-95.9)	82.8 (70.9-94.6)
No bleeding	53.1 (45.1-61.1)	79.7 (72.3-87)	90.6 (85.1-96.1)	93 (88.1-97.9)
In-hospital death ($P = .0440$)				
Bleeding	3.4 (0-7.4)	6.9 (1.4-12.4)	6.9 (0.2-13.6)	10.3 (2.6-18.1)
No bleeding	0 (0-0)	0 (0-1.3)	1.6 (0-3.8)	1.6 (0-3.8)

Estimated probability of either discharge or in-hospital death is provided for days 15, 30, 60, and 90 postoperatively, and the 95% confidence interval is in parentheses. P value is provided for comparing the bleeders and nonbleeders.³¹