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Severe Postoperative Bleeding after Heart Transplantation

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Postoperative bleeding is a frequent complication after cardiac surgery, particularly in procedures involving cardiopulmonary bypass

What This Article Tells Us That Is New

- Severe hemorrhagic complications after heart transplantation occur commonly, especially among patients who require mechanical circulatory support
- Severe postoperative bleeding after heart transplantation is associated with substantially increased morbidity and mortality

ABSTRACT

Background: Postoperative bleeding is frequent in cardiac surgery, but its incidence, risk factors, and consequences remain largely unknown after heart transplantation. The main objective of this study was to describe the incidence of severe bleeding complications after adult heart transplantation.

Methods: The authors conducted an observational study including all adult patients who received a heart transplant between 2015 and 2022 in two French referral centers. The primary endpoint was the incidence of severe bleeding complications defined by a Universal Definition of Perioperative Bleeding score of 3 or greater. Multivariable logistic regression was used to identify variables associated with the incidence of severe postoperative bleeding. The impact of severe postoperative bleeding on 1-yr mortality was evaluated using a multivariable Cox regression model.

Results: Among the 446 patients included, 112 (25%) developed severe bleeding. In multivariable analysis, long-term mechanical cardiac support (adjusted odds ratio [adjOR; 95% CI], 2.21 [1.01 to 4.88]), preoperative hemoglobin (adjOR, 0.85 [0.76 to 0.95]) and the duration of cardiopulmonary bypass (per 10-min increase; adjOR, 1.08 [1.03 to 1.15]) were associated with severe bleeding. Severe postoperative bleeding was associated with an increased mortality at 1 yr (35% *vs.* 13%; $P < 0.001$), with an adjusted hazard ratio of 1.91 (95% CI, 1.18 to 3.09; $P = 0.008$).

Conclusions: This study reports a high incidence of severe hemorrhagic complications after heart transplantation, particularly in patients with mechanical circulatory support. Bleeding complications were associated with a significant increase in morbidity and mortality. Larger-scale studies are needed to identify and evaluate potential prevention strategies.

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Abbreviations: adjOR, adjusted odds ratio; **CPB**, cardiopulmonary bypass; **DOAC**, direct oral anticoagulant; **ECMO**, extracorporeal membrane oxygenation; **FFP**, fresh frozen plasma; **HMS**, heparin management system; **ICU**, intensive care unit; **MCS**, mechanical circulatory support; **PGD**, primary graft dysfunction; **UDPB**, Universal Definition of Perioperative Bleeding; **VKA**, vitamin K antagonist

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Postoperative bleeding is a common complication in cardiac surgery, especially using cardiopulmonary bypass (CPB).[1] Its mechanisms are multifactorial, involving surgical factors, antithrombotic exposure, and CPB-related hemostatic disorders and hemodilution.[2,3] While often mild, severe postoperative bleeding—although less frequent—is a major complication, linked to increased morbidity and mortality,[4–6] and contributes significantly to transfusion requirements, with cardiac surgery accounting for 10 to 15% of all transfusions in the United States.[7] Several bleeding classifications have been developed.[8] Among them, the Universal Definition of Perioperative Bleeding (UDPB) categorizes bleeding into five classes based on nine clinical variables occurring intraoperatively or within the first postoperative day.[4] Classes 3 and 4 define severe bleeding, which is associated with the use of factor concentrates, allogeneic transfusions, and increased morbidity and mortality.[4,8]

International guidelines on patient blood management in cardiac surgery recommend strategies to reduce perioperative bleeding.[1,9,10] These include identifying at-risk patients, managing antithrombotic drugs preoperatively, optimizing CPB, and using algorithm-guided therapy for perioperative bleeding.

Heart transplantation is the primary treatment for end-stage heart failure, offering improved survival and quality of life.[11] More than 6,000 transplants are performed annually worldwide, with a 1-yr survival rate around 85% and a median survival exceeding 12 yr.[12] In France, approximately 400 heart transplants are performed each year across 24 referral university hospitals.[13] Posttransplant survival has improved during the past two decades, mainly due to reduced early mortality. However, the intra- and postoperative periods remain at high risk due to the increased use of mechanical circulatory support and a higher proportion of sensitized patients.[14]

The incidence and impact of severe bleeding after heart transplantation remain poorly understood. Moreover, heart transplant patients are largely underrepresented in prospective trials on bleeding and transfusion in cardiac surgery.[15–18] To date, only two adult studies have addressed this issue. A Korean retrospective single-center study found that transfusion of more than 6 units of red blood cells intraoperatively and within the first 24 h postoperatively was associated with increased long-term mortality.[19] A second study in 2020 reported that 1 unit of red blood cells transfused increased all-cause mortality at 30 days by 30%.[20]

Few studies have examined postoperative bleeding after heart transplantation, and its risk factors and consequences remain largely unknown. The primary objective of this study was therefore to describe the incidence of severe bleeding complications after heart transplantation. Secondary objectives included describing perioperative hemostasis and transfusion practices, identifying factors associated with the occurrence of severe bleeding, and evaluating its impact on postoperative outcomes.

Materials and Methods

Study Design and Population

All consecutive adult patients (18 yr or older) who underwent heart transplantation from January 2015 to December 2022 and were subsequently hospitalized in the cardiothoracic surgical intensive care unit (ICU) at the two participating centers (University Hospital of Rennes, Rennes, France; and Pitié-Salpêtrière University Hospital, Paris, France) were included; no patients were excluded. Data were collected by research assistants from medical records (paper or electronic) and followed from the day of surgery to death or discharge from the hospital and up to 1 yr for survival status. Data included patient characteristics and comorbidities, surgery and anesthesia management, postoperative ICU management, complications, and outcomes. This study has been ethically approved (University Hospital of Rennes ethics committee No. 24.58). According to the French legislation, written consent was waived because of the observational design of the study. The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplemental Digital Content table S1, https://links.lww.com/ALN/E386).

Outcomes and Variables

Our primary outcome was the incidence of severe perioperative bleeding defined as a UDPB score of 3 to 4, measured from the time of sternal closure.[4,21] Secondary outcomes were UDPB classes (0 to 4) and their components, including perioperative allogeneic transfusion and factor concentrates use, ICU length of stay, in-hospital mortality, mortality at day 30, and 1-yr mortality. The UDPB score was calculated according to the original publication and as reported in Supplemental Digital Content table S2 (https://links.lww.com/ALN/E386).[4] In addition, the following variables were included in the

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current study: preoperative patient-related variables (baseline demographics and comorbidities, antithrombotic drugs, mechanical circulatory support, laboratory results), intraoperative variables (CPB management, hemostasis and transfusion management), and postoperative variables (hemostasis and transfusion management, major postoperative morbidity). In cases of refractory intraoperative bleeding, the anesthesia and surgical teams could jointly decide to perform delayed sternal closure, as defined by the UDPB score, by closing the sternum with chest packing at the end of the procedure. Primary graft dysfunction (PGD) was defined according to the International Society for Heart and Lung Transplantation (Chicago, Illinois) consensus.[22]

Patient Management

Patients were managed in the cardiothoracic department of two tertiary university hospitals, comprising both cardiothoracic surgery and cardiothoracic surgical ICU. Patient management remained consistent throughout the study inclusion period and followed international guidelines.[11] Patients received an immunosuppressive therapy consisting of a combination of tacrolimus, mycophenolate mofetil, and prednisolone. Induction therapy was performed using either basiliximab or antithymocyte globulins. Maintenance of anesthesia was performed using total intravenous anesthesia. Standard monitoring, transesophageal echocardiography, and invasive arterial blood pressure measurement were uniformly employed during all heart transplant procedures. All patients underwent CPB using roller pumps using a pH-stat strategy, with a target mean arterial blood pressure between 60 and 80 mmHg.

Institutional practices regarding the chronic management of antithrombotic therapy, reversal strategies at the time of transplantation, and perioperative hemostasis and transfusion management remained consistent throughout the study period and followed international patient blood management guidelines.[1,11] Aspirin was preferred instead of P2Y12 inhibitors for chronic antiplatelet therapy. When dual antiplatelet therapy was indicated, thienopyridines (clopidogrel, prasugrel) were preferred instead of ticagrelor. Chronic oral anticoagulation was preferentially managed with vitamin K antagonist (VKA) rather than direct oral anticoagulants (DOACs). VKAs were reversed during surgery using intravenous vitamin K and international normalized ratio–guided four-factor prothrombin complex concentrates. DOACs were reversed using prothrombin complex concentrates.[23] Intraoperative antifibrinolytics (tranexamic acid or aprotinin) were used systematically. Aprotinin has been used off label at the discretion of the anesthesiologist since 2016 as part of the European Nordic Aprotinin Patient Registry (NAPaR) postauthorization safety study.[24] Intravenous unfractionated heparin was administered after sternotomy to maintain an activated clotting time greater than 400 s, monitored using Hemochron Signature Elite (Werfen, France) or the Hepcon Heparin Management System (HMS) Plus (Medtronic, France). Heparin was fully reversed by protamine sulfate using either a fixed ratio approach or HMS protamine titration. Cell salvage was performed intraoperatively for all procedures using the Xtra device (Livanova, United Kingdom). Intraoperative red blood cell transfusion and hemofiltration were considered to maintain a hemoglobin greater than 7 g $\cdot$ dl^{-1} and/or oxygen delivery greater than 280 ml $\cdot$ min^{-1} $\cdot$ m^{-2}. Perioperative bleeding and transfusion management followed goal-directed hemostatic algorithms based on either fast-track conventional coagulation tests or viscoelastic testing (ROTEM Delta, Werfen, France; QUANTRA, Stago BioCare, France). The decision to reexplore for bleeding was based on blood loss volume, hemodynamic stability, hemoglobin levels, and echocardiographic findings.

Statistical Analysis

Patient characteristics are expressed as number (proportion) for categorical variables and median (interquartile range) for continuous variables. For bivariate comparison between severe and nonsevere bleeding, a chi-square test or a Fisher exact test was used for categorical variables and a Wilcoxon rank sum test for continuous variables. A statistical analysis plan was made before accessing the data. No *a priori* statistical power calculation was conducted. All analyses were conducted on complete cases. All tests used a two-tailed hypothesis. Statistical significance was achieved for $P < 0.05$. Statistical analyses were performed using R 4.4.1 statistical software (https://www.r-project.org, accessed June 1, 2024).

Multivariable logistic regression models were used to identify pre- and intraoperative variables associated with the incidence of severe postoperative bleeding. Variables entered in the models were defined *a priori*, based on extensive review of literature investigating postoperative bleeding in cardiac surgery.[25–29] No further variable selection was done. The set of variables entered in the first model (model 1) was age, sex, body mass index, preoperative VKA, preoperative DOAC, preoperative aspirin, preoperative P2Y12 inhibitor, redo surgery, long-term mechanical circulatory support (support with a left ventricular assist device or a total artificial heart at the time of transplantation, irrespective of the duration between device implantation and transplantation), extracorporeal membrane oxygenation (ECMO) bridge to transplantation, preoperative platelets, preoperative hemoglobin, preoperative bilirubin, and study center. Due to a sample size being insufficient, we decided not to adjust the multivariable analysis for the year of transplantation after carrying out an analysis of bleeding severity by year, demonstrating no relationship between the year of transplantation and the occurrence of severe postoperative bleeding (Supplemental Digital Content fig. S1, https://links.lww.com/ALN/E386). A second model (model 2) was built as a sensitivity analysis by removing two variables (preoperative DOAC and preoperative P2Y12 inhibitor) for which the number of events was low. Absence of

multicollinearity and linearity of continuous variables and log-odds was checked. Treatment effect was expressed as odds ratio with corresponding 95% CI.

Kaplan–Meier survival curves with log-rank test were used to compare survival according to UDPB classification. A directed acyclic graph was used to describe the relationships between severe perioperative bleeding (exposure variables), patient-related confounders, surgery-related confounders, and 1-yr mortality using DAGitty software (V3.1, https://www.dagitty.net, accessed June 1, 2024; Supplemental Digital Content fig. S2, https://links.lww.com/ALN/E386). No variables were analyzed as effect modifiers. The set of potential confounders sufficient for adjustment was preoperative anemia (evaluated by preoperative hemoglobin level), liver failure (evaluated by preoperative bilirubin level), CPB duration, and early postoperative ECMO support (defined as ECMO cannulation less than 12 h postoperatively). A multivariable Cox regression model, stratified by center, was then used to estimate the total effect of severe postoperative bleeding on 1-yr mortality, adjusting for the confounders defined *a priori* using the directed acyclic graph.

Results

Study Population

The study included all 446 patients who underwent heart transplantation between January 1, 2015, and December 31, 2022 (fig. 1). The preoperative characteristics are reported in table 1. The median age was 58 (49 to 66) yr, 24% of patients were women, and the median body mass index was 24.8 (22.4 to 28.1) kg · m^{-2}. The leading heart failure etiology was ischemic cardiomyopathy (41%), followed by dilated cardiomyopathy (34%). Before heart transplantation, 52% of patients received anticoagulant treatment with VKA, 2% received DOAC, and 18% received therapeutic heparin. Of the patients, 41% had previous open cardiac surgery. Of 70 patients on long-term mechanical circulatory support, 54 (12%) were supported by a left ventricular assist device and 16 (4%) by a total artificial heart. No patient was supported by short-term mechanical circulatory support alone. In the preoperative period, 4% required mechanical ventilation, 26% required inotropic dobutamine support, and 1% received renal replacement therapy.

Intraoperative Management

Surgery-related characteristics are reported in table 2. The median total ischemic time was 205 (175 to 232) min, and the median duration of CPB was 121 (104 to 147) min. The lowest intraoperative hematocrit was 26% (22 to 30). Inotropic and vasopressor support included a maximum dobutamine dose of 8 (5 to 10) μg · kg^{-1} · min^{-1} and a norepinephrine dose of 0.3 (0.1 to 0.7) μg · kg^{-1} · min^{-1}. Allogeneic transfusions were frequently required: 63% of patients received red blood cell transfusion with a median of 4 (2 to 6) units, 72% received fresh frozen plasma (FFP)

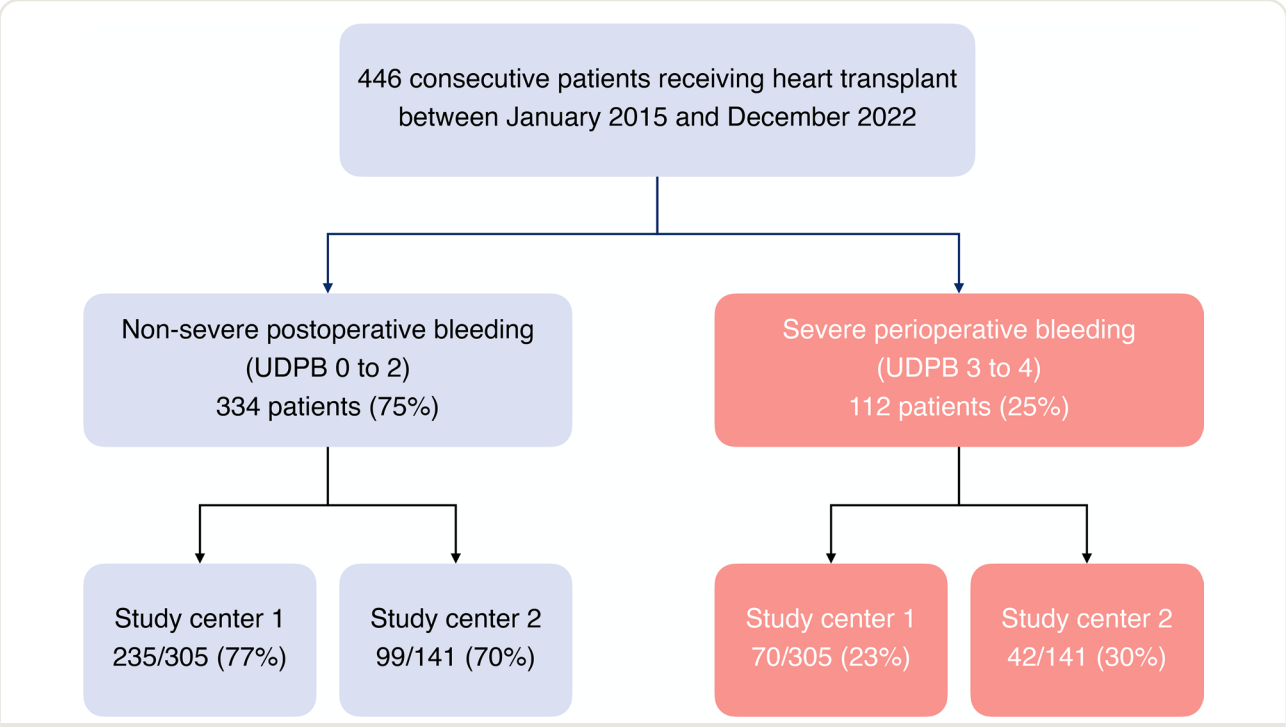

Fig. 1. Flowchart of heart transplant patients included in the study. UDPB, Universal Definition of Perioperative Bleeding.

Table 1. Patient Characteristics at the Time of Heart Transplantation

Characteristic	No.	All Patients (n = 446)	Nonsevere Bleeding (n = 334)	Severe Bleeding (n = 112)	*P* Value
Age, yr	446	58 (49–66)	58 (49–66)	56 (48–65)	0.501
Female sex	446	106 (24%)	84 (25%)	22 (20%)	0.236
Body mass index, kg · m^{-2}	446	24.8 (22.4–28.1)	25.0 (22.1–28.3)	24.6 (22.7–27.4)	0.997
Comorbidities					
Hypertension	446	125 (28%)	86 (26%)	39 (35%)	0.064
Diabetes	446				0.351
Non–insulin-dependent diabetes		62 (14%)	48 (14%)	14 (13%)	
Insulin-dependent diabetes		9 (2.0%)	5 (1.5%)	4 (3.6%)	
Atrial fibrillation	441	152 (34%)	114 (35%)	38 (34%)	0.890
Peripheral artery occlusive disease	446	24 (5.4%)	18 (5.4%)	6 (5.4%)	0.990
Chronic kidney disease	446	114 (26%)	86 (26%)	28 (25%)	0.875
Stroke	441	70 (16%)	51 (16%)	19 (17%)	0.714
Antithrombotic drugs					
Therapeutic heparin	440	79 (18%)	49 (15%)	30 (27%)	0.005
Acetylsalicylic acid	439	126 (29%)	90 (28%)	36 (32%)	0.351
P2Y12 inhibitors	439	25 (5.7%)	20 (6.1%)	5 (4.5%)	0.515
VKA	439	229 (52%)	178 (54%)	51 (46%)	0.104
DOAC	439	9 (2.1%)	6 (1.8%)	3 (2.7%)	0.699
Mechanical circulatory support					
Long-term MCS	446				< 0.001
Left ventricular assist device		54 (12%)	32 (9.6%)	22 (20%)	
Total artificial heart		16 (3.6%)	7 (2.1%)	9 (8.0%)	
ECMO bridge to transplantation	446	75 (17%)	52 (16%)	23 (21%)	0.224
Intra-aortic balloon pump	446	16 (3.6%)	10 (3.0%)	6 (5.4%)	0.248
Preoperative state					
Redo surgery	446	183 (41%)	129 (39%)	54 (48%)	0.074
Mechanical ventilation	446	16 (3.6%)	11 (3.3%)	5 (4.5%)	0.562
Dobutamine use	440	116 (26%)	82 (25%)	34 (30%)	0.267
Renal replacement therapy	440	6 (1.4%)	1 (0.3%)	5 (4.5%)	0.005
Preoperative laboratory results					
Hemoglobin, g · dl^{-1}	446	12.3 (10.2–13.8)	12.5 (10.6–14.0)	11.2 (9.0–13.1)	< 0.001
Hematocrit, %	437	36 (31–41)	37 (31–42)	35 (29–40)	0.043
Platelets, g · l^{-1}	440	202 (158–253)	201 (162–253)	204 (152–258)	0.969
INR	375	1.8 (1.2–2.5)	1.8 (1.2–2.5)	1.8 (1.2–2.5)	0.656
Creatinine, µmol · l^{-1}	446	105 (84–137)	105 (84–137)	104 (85–136)	0.984
Bilirubin, mg · l^{-1}	446	13 (8–22)	13 (8–22)	14 (8–23)	0.893
AST, U · l^{-1}	436	33 (24–48)	32 (25–49)	33 (23–45)	0.361

Results are presented as n (%) or median (interquartile range). Nonsevere bleeding was defined as UDPB score 0 to 2; severe bleeding was defined as UDPB score 3 to 4.

AST, aspartate aminotransferase; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; INR, international normalized ratio; MCS, mechanical circulatory support; VKA, vitamin K antagonist.

with a median of 4 (3 to 6) units, 61% received platelet concentrate transfusion with a median of 1 (1 to 2) unit, 43% received fibrinogen concentrate, and 53% received prothrombin complex concentrate.

Postoperative Bleeding and Description of UDPB Variables

Overall, 112 (25%) patients developed severe bleeding, as characterized by a UDPB score of 3 and 4. Bleeding incidences based on UDPB classes are reported in Supplemental Digital Content table S3 (https://links.lww.com/ALN/E386). Bleeding-related variables included in UDPB classification (transfusion of blood products, reexploration for bleeding, and blood loss) are summarized in table 3. In the initial 24 h after sternal closure, 35% of patients received red blood cell transfusions, 29% were given FFP, and 24% were administered platelet concentrate. The median chest tube output was 420 (240 to 740) ml for the first 12 h and 655 (383 to 1,173) ml during 24 h. Fibrinogen and prothrombin complex concentrates were used, respectively, for 13% and 4% during the first 24 h. In addition, 1% of patients received recombinant factor VIIa concentrate due to uncontrolled severe bleeding. The surgical team opted for a delayed sternal closure in 2% of patients and an early reintervention for bleeding was deemed necessary for 13% of patients within the first 24 h. As anticipated, patients with severe bleeding demonstrated worsened outcomes across all variables of the UDPB classification (table 3).

Table 2. Intraoperative Management

Characteristic	No.	All Patients (n = 446)	Nonsevere Bleeding (n = 334)	Severe Bleeding (n = 112)	*P* Value
Surgery and CPB					
Graft ischemia time, min	442	205 (175–232)	202 (171–228)	217 (190–245)	0.002
Duration of CPB, min	443	121 (104–147)	120 (103–144)	127 (107–167)	0.008
Duration of clamping, min	440	73 (61–88)	72 (60–87)	77 (64–97)	0.014
Major vascular injury	440	39 (8.9%)	21 (6.4%)	18 (16%)	0.002
Lowest hematocrit, %	410	26 (22–30)	27 (23–31)	23 (21–27)	< 0.001
Lowest pH	409	7.32 (7.26–7.38)	7.33 (7.27–7.38)	7.28 (7.23–7.35)	< 0.001
Maximum dobutamine dose, μg · kg^{-1} · min^{-1}	444	8 (5–10)	8 (5–10)	10 (5–12)	0.012
Maximum norepinephrine dose, μg · kg^{-1} · min^{-1}	439	0.3 (0.1–0.7)	0.3 (0.1–0.5)	0.5 (0.2–0.9)	< 0.001
Hemostasis and transfusion					
Intraoperative blood salvage, ml · kg^{-1}	354	9 (5–14)	7 (5–12)	11 (8–19)	< 0.001
Total UFH dose, U · kg^{-1}	427	412 (341–502)	408 (333–500)	427 (357–541)	0.042
Total protamine dose, U · kg^{-1}	422	333 (244–419)	325 (242–417)	352 (250–423)	0.163
Protamine/UFH ratio	422	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.9 (0.6–1.0)	0.742
Total tranexamic acid dose, mg · kg^{-1}	349	32 (26–40)	31 (26–39)	32 (27–42)	0.592
Use of aprotinin	426	85 (20%)	68 (21%)	17 (16%)	0.187
Red blood cell transfusion	446	279 (63%)	187 (56%)	92 (82%)	< 0.001
Units transfused	279	4 (2–6)	3 (2–5)	6 (4–8)	< 0.001
FFP transfusion	446	319 (72%)	221 (66%)	98 (88%)	< 0.001
Units transfused	319	4 (3–6)	4 (3–5)	6 (4–8)	< 0.001
PC transfusion	446	273 (61%)	183 (55%)	90 (80%)	< 0.001
Units transfused*	273	1 (1–2)	1 (1–2)	2 (1–2)	< 0.001
PCC	446	237 (53%)	176 (53%)	61 (54%)	0.745
PCC quantity, U · kg^{-1}	237	27 (21–40)	27 (21–39)	31 (22–47)	0.274
Fibrinogen concentrate	446	194 (43%)	118 (35%)	76 (68%)	< 0.001
Fibrinogen quantity, mg · kg^{-1}	189	37 (26–48)	34 (25–45)	42 (31–52)	0.007
rFVIIa concentrate	439	8 (1.8%)	0 (0%)	8 (7.1%)	< 0.001

Results are presented as n (%) or median (interquartile range). Nonsevere bleeding was defined as UDPB score 0 to 2; severe bleeding was defined as UDPB score 3 to 4. Intraoperative period was considered from anesthesia induction to sternal closure.

*French apheresis or pooled platelet concentrates, equivalent to 6 platelet units.

CPB, cardiopulmonary bypass; FFP, fresh frozen plasma; PC, platelet concentrate; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; UFH, unfractionated heparin.

Factors Associated with the Occurrence of Severe Postoperative Bleeding

Compared to nonsevere bleeding patients (tables 1 and 2), those with severe postoperative bleeding more likely underwent redo surgery (48% *vs.* 39%; $P = 0.074$), were receiving preoperative renal replacement therapy (4.5% *vs.* 0.3%; $P = 0.005$), and were more frequently supported by long-term mechanical circulatory support (MCS; 28% *vs.* 12%; $P < 0.001$). Preoperative anemia was also more frequent, with a median of 11.2 (9.0 to 13.1) g · dl^{-1} and 12.5 (10.6 to 14.0) g · dl^{-1} ($P < 0.001$), respectively, for severe and nonsevere bleeding patients. Additionally, severe bleeding was associated with longer CPB durations (127 [107 to 167] min *vs.* 120 [103 to 144] min; $P = 0.008$) and lower intraoperative hematocrit (23 [21 to 27]% *vs.* 27 [23 to 31]%; $P < 0.001$). Finally, bleeding patients were more likely to receive allogeneic transfusion, large intraoperative blood salvage volumes, and factor concentrates (table 2). Univariable logistic regression analyses for severe postoperative bleeding are reported in Supplemental Digital Content table S4 (https://links.lww.com/ALN/E386). In multivariable analysis, the factors associated with the occurrence of severe bleeding events after adjustment were long-term mechanical circulatory support (adjusted odds ratio [adjOR], 2.21 [1.01 to 4.88]), preoperative hemoglobin (adjOR, 0.85 [0.76 to 0.95]), and the duration of CPB (per 10-min increase; adjOR, 1.08 [1.03 to 1.15]; table 4).

Impact of Severe Bleeding on Postoperative Outcomes

Outcomes after heart transplantation are detailed in table 5. The median ICU stay was 13 (9 to 23) days, and the duration of mechanical ventilation was 2 (1 to 5) days. Moderate to severe PGD was reported in 73% of patients, and 48% of the cohort received early veno-arterial-ECMO support, either in the operating room or within 12 h after surgery. Acute kidney failure required renal replacement therapy for 29% of patients. Severe postoperative bleeding was associated with poorer outcomes including a higher incidence of PGD (87% *vs.* 68%; $P < 0.001$), increased early postoperative ECMO support (76% *vs.* 39%; $P < 0.001$), and a greater need for renal replacement therapy (46% *vs.* 23%; $P < 0.001$). In addition, they experienced more ventilator-associated pneumonia, stroke, and atrial fibrillation, and had longer ICU length of stay.

Table 3. Description of UDPB Score Variables

Characteristic	No.	All Patients (n = 446)	Nonsevere Bleeding (n = 334)	Severe Bleeding (n = 112)	*P* Value*
Chest tube output					
During the first 12 h, ml	437	420 (240–740)	333 (220–510)	1,290 (870–1,850)	< 0.001
During the first 12 h, ml · kg^{-1}	443	5 (3–11)	4 (3–7)	18 (11–25)	< 0.001
During the first 24 h, ml	435	655 (383–1,173)	520 (345–780)	1,760 (1,250–2,550)	< 0.001
During the first 24 h, ml · kg^{-1}	441	8 (5–16)	7 (4–11)	26 (15–34)	< 0.001
Red blood cell transfusion					
Transfusion during the first 24 h	446	154 (35%)	62 (19%)	92 (82%)	< 0.001
Transfusion during the hospitalization	446	307 (69%)	207 (62%)	100 (89%)	< 0.001
Total units during the hospitalization	446	2 (0–4)	1 (0–2)	4 (4–5)	< 0.001
FFP transfusion					
Transfusion during the first 24 h	446	131 (29%)	49 (15%)	82 (73%)	< 0.001
Transfusion during the hospitalization	446	150 (34%)	81 (24%)	69 (62%)	< 0.001
Total units during the hospitalization	446	2 (0–5)	0 (0–2)	5 (5–6)	< 0.001
PC transfusion					
Transfusion during the first 24 h	446	106 (24%)	32 (9.6%)	74 (66%)	< 0.001
Transfusion during the hospitalization	446	188 (42%)	106 (32%)	82 (73%)	< 0.001
Total units during the hospitalization†	446	1 (0–4)	0 (0–4)	9 (3–9)	< 0.001
Fibrinogen concentrate					
Use during the first 24 h	440	57 (13%)	16 (4.9%)	41 (37%)	< 0.001
Use during the hospitalization	439	64 (15%)	31 (9.5%)	33 (30%)	< 0.001
Total quantity during the hospitalization, mg · kg^{-1}	426	0 (0–22)	0 (0–24)	0 (0–18)	0.652
PCC					
Use during the first 24 h	439	18 (4.1%)	5 (1.5%)	13 (12%)	< 0.001
Use during the hospitalization	440	15 (3.4%)	4 (1.2%)	11 (9.8%)	< 0.001
Total quantity during the hospitalization, U · kg^{-1}	446	0 (0–0)	0 (0–0)	0 (0–0)	0.013
Use of rFVIIa concentrate during the first 24 h	440	3 (0.7%)	0 (0%)	3 (2.7%)	0.016
Delayed sternal closure	440	10 (2.3%)	0 (0%)	10 (8.9%)	< 0.001
Surgical reexploration < 24 h	440	59 (13%)	0 (0%)	59 (53%)	< 0.001

Results are presented as n (%) or median (interquartile range). Nonsevere bleeding was defined as UDPB score 0 to 2; severe bleeding was defined as UDPB score 3 to 4. Intraoperative period was considered from anesthesia induction to sternal closure.

**P* values for continuous variables derived from Wilcoxon rank-sum test; zero inflation may reduce power and reflect differences in transfusion occurrence rather than quantity.
†French apheresis or pooled platelet concentrates, equivalent to 6 platelet units.

FFP, fresh frozen plasma; PC, platelet concentrate; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; UDPB, Universal Definition of Perioperative Bleeding.

In-hospital mortality was 15% and reached 19% at 1 yr (table 5). Severe postoperative bleeding was associated with an increased mortality at 1 yr (35% *vs.* 13%; $P < 0.001$) corresponding to threefold higher hazard, with an unadjusted hazard ratio of 3.18 (95% CI, 2.07 to 4.90; $P < 0.001$). The decline in survival was mainly observed during the first 30 postoperative days (fig. 2). After adjustment for preoperative hemoglobin, preoperative bilirubinemia, duration of CPB, and early postoperative ECMO support, severe postoperative bleeding was associated with increased mortality (adjusted hazard ratio, 1.91; 95% CI, 1.18 to 3.09; $P = 0.008$; Supplemental Digital Content table S5, https://links.lww.com/ALN/E386). Analysis based on the UDPB class (ranging from 0 to 4) yielded consistent results in both the unadjusted and multivariable analyses (Supplemental Digital Content table S3 and fig. S3, https://links.lww.com/ALN/E386).

Discussion

Our study reported perioperative bleeding in a large two-center cohort of heart transplant recipients. The main findings were as follows. First, one in four patients experienced severe postoperative bleeding according to UDPB classification. Second, after adjustment, severe bleeding events were associated with longer CPB durations, preoperative anemia, and long-term MCS support. Third, adjusted time-to-event analysis revealed a clinically relevant effect of severe bleeding on 1-yr mortality.

Postoperative bleeding in heart transplantation is a complex issue, influenced by many different factors, including the preoperative clinical condition, intraoperative management of CPB, surgical techniques, and patient blood management strategies.[30] Despite significant improvement in transfusion and hemostasis management in cardiac surgery, it remains impossible to entirely avoid postoperative bleeding.[1,9,10] It is therefore mandatory to establish its prevalence through a precise clinical definition to facilitate the conduct of clinical studies and ultimately to improve the prognosis of patient.[4,11,31] To this end, we chose the UDBP score, which is now validated in cardiac surgery.[4] Thus, several studies have demonstrated excellent discrimination in terms of the severity of bleeding and a strong correlation

Table 4. Factors Associated with the Occurrence of Severe Bleeding Events in Multivariable Logistic Regression

	Model 1			Model 2		
Variables	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Age, yr	1.00	0.99–1.01	0.762	1.00	0.99–1.01	0.819
Female sex	0.80	0.45–1.39	0.445	0.80	0.45–1.38	0.425
Body mass index, kg · m^{-2}	0.99	0.93–1.05	0.680	0.99	0.93–1.04	0.670
Preoperative VKA	0.66	0.39–1.13	0.132	0.66	0.39–1.11	0.116
Preoperative DOAC	1.56	0.31–6.42	0.548	—	—	—
Preoperative aspirin	1.05	0.61–1.76	0.866	1.02	0.60–1.70	0.950
Preoperative P2Y12 inhibitor	0.74	0.22–2.07	0.588	—	—	—
Redo surgery	0.96	0.52–1.74	0.894	0.96	0.52–1.74	0.894
Long-term MCS	2.21	1.01–4.88	0.048	2.22	1.02–4.91	0.046
ECMO bridge to transplantation	0.98	0.49–1.93	0.964	0.99	0.49–1.94	0.976
Preoperative platelets, g · l^{-1}	1.00	1.00–1.00	0.723	1.00	1.00–1.00	0.706
Preoperative hemoglobin, g · dl^{-1}	0.85	0.76–0.95	0.003	0.85	0.77–0.95	0.004
Preoperative bilirubin, mg · l^{-1}	1.00	0.99–1.02	0.544	1.01	0.99–1.02	0.507
Duration of CPB (per 10-min increase)	1.08	1.03–1.15	0.003	1.09	1.03–1.15	0.003
Study center	1.11	0.63–1.92	0.719	1.11	0.64–1.92	0.708

Results are presented as odds ratio (OR) with 95% CI. Model 1 and model 2 were multivariable logistic regression including all reported variable (except for preoperative VKA and P2Y12 inhibitors for model 2). Preoperative P2Y12 inhibitor: clopidogrel, prasugrel, and ticagrelor.

CPB, cardiopulmonary bypass; DOAC, direct oral anticoagulant; ECMO, extracorporeal membrane oxygenation; MCS, mechanical circulatory support (left ventricular assist device and total artificial heart); VKA, vitamin K antagonist.

of UDPB categories with postoperative outcomes, including mortality.[8,21,32] This classification strictly pertains to bleeding events occurring during the early postoperative phase (from sternal closure), thereby excluding preoperative, intraoperative, and late postoperative transfusions. Our study confirmed the ability of the UDPB score to classify and define the severity of postoperative hemorrhagic events after cardiac transplantation.

No study has precisely examined severe postoperative bleeding after heart transplantation using a valid definition such as the UDPB classification. Two studies quantified the degree of bleeding after heart transplantation by the number of packed red blood cells transfused, focusing on the effects of transfusion on postoperative outcomes and mortality without accurately describing the incidence of bleeding.[19,20] Yet Nam *et al.* reported that 29% of patients received more than 6 units of red blood cells during admission for heart transplant.[19] In prospective trials focusing on bleeding and transfusion in cardiac surgery, heart transplant recipients are significantly underrepresented and rarely studied.[15–18,33,34] Although noncomparative, our study suggests that heart transplantation is associated with a higher rate of severe postoperative bleeding compared to conventional cardiac surgery. Supporting this, a recent study conducted in Mexico investigated the incidence of bleeding in cardiac surgery using the UDPB score and found that 12% of cardiac surgery patients (mainly undergoing valve surgeries) experienced severe bleeding, defined by a UDPB score of 3 to 4.[35] Similarly, Dyke *et al.* reported a 10% incidence of severe bleeding,[4] while a large cohort study involving more than 7,000 cardiac surgery patients reported a 24% incidence according to UDPB.[32] However, comparing with other studies can be challenging because the UDPB classification still largely depends on centers' practices (transfusion thresholds, use of coagulation factors, readiness to reoperate).

We identified three factors associated with the occurrence of severe postoperative bleeding after adjustment. First, the duration of CPB is a well-described risk factor in cardiac surgery, associated with allogeneic transfusion requirements, drainage tube output, and reintervention for bleeding.[36,37] In addition to highlighting the complexity of the surgical procedure and potential operative complications, the duration of CPB is itself associated with an increased inflammatory response and platelet functional defects, which can contribute to the pathophysiology of bleeding.[38] Second, preoperative anemia is also well described as a risk factor for postoperative bleeding.[28,39] Preoperative anemia contributes to excessive hemodilution during CPB, a condition associated with coagulopathy and postoperative bleeding.[40] However, determining the direct contribution of anemia remains challenging due to the numerous confounding factors associated with disease severity and the patient's overall condition. Third, the preoperative use of long-term MCS was associated with severe postoperative bleeding. The improvements in end-stage heart failure management and the limited supply of donor hearts are responsible for a rising number of patients supported by long-term MCS.[41,42] MCS can contribute to bleeding through multiple mechanisms. The thrombotic risk associated with MCS justifies the use of oral anticoagulation and antiplatelet agents that may contribute to an increased bleeding risk.[43] In addition, MCS is frequently

Table 5. Postoperative Outcomes

Characteristic	No.	All Patients (n = 446)	Nonsevere Bleeding (n = 334)	Severe Bleeding (n = 112)	*P* Value
Postoperative morbidity					
Moderate to severe PGD	444	322 (73%)	225 (68%)	97 (87%)	< 0.001
ECMO after CPB (< 12 h)	445	215 (48%)	130 (39%)	85 (76%)	< 0.001
Maximum dobutamine dose, μg · kg^{-1} · min^{-1}	438	8 (5–10)	8 (5–10)	10 (5–13)	0.057
Duration of dobutamine use, days	437	7 (4–11)	7 (4–11)	8 (5–13)	0.048
Maximum norepinephrine dose, μg · kg^{-1} · min^{-1}	431	0.4 (0.1–0.9)	0.3 (0.1–0.7)	0.8 (0.4–1.6)	< 0.001
Atrial fibrillation	446	51 (11%)	31 (9.3%)	20 (18%)	0.014
Renal replacement therapy	446	129 (29%)	78 (23%)	51 (46%)	< 0.001
Duration of mechanical ventilation, days	444	2 (1–5)	2 (1–4)	4 (2–12)	< 0.001
Stroke	446	32 (7.2%)	15 (4.5%)	17 (15%)	< 0.001
Ventilator-associated pneumonia	446	161 (36%)	103 (31%)	58 (52%)	< 0.001
Mediastinitis	445	36 (8.1%)	25 (7.5%)	11 (9.8%)	0.437
Bacteremia	445	108 (24%)	80 (24%)	28 (25%)	0.835
Length of stay in intensive care unit, days	446	13 (9–23)	12 (9–20)	18 (11–31)	< 0.001
Mortality					
In-hospital mortality	446	69 (15%)	30 (9.0%)	39 (35%)	< 0.001
Mortality at day 30	446	49 (11%)	20 (6.0%)	29 (26%)	< 0.001
One-year mortality	446	83 (19%)	44 (13%)	39 (35%)	< 0.001

Results are presented as n (%) or median (interquartile range). Nonsevere bleeding was defined as UDPB score 0 to 2; severe bleeding was defined as UDPB score 3 to 4. Intraoperative period was considered from anesthesia induction to sternal closure.

CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; PGD, primary graft dysfunction; UDPB, Universal Definition of Perioperative Bleeding.

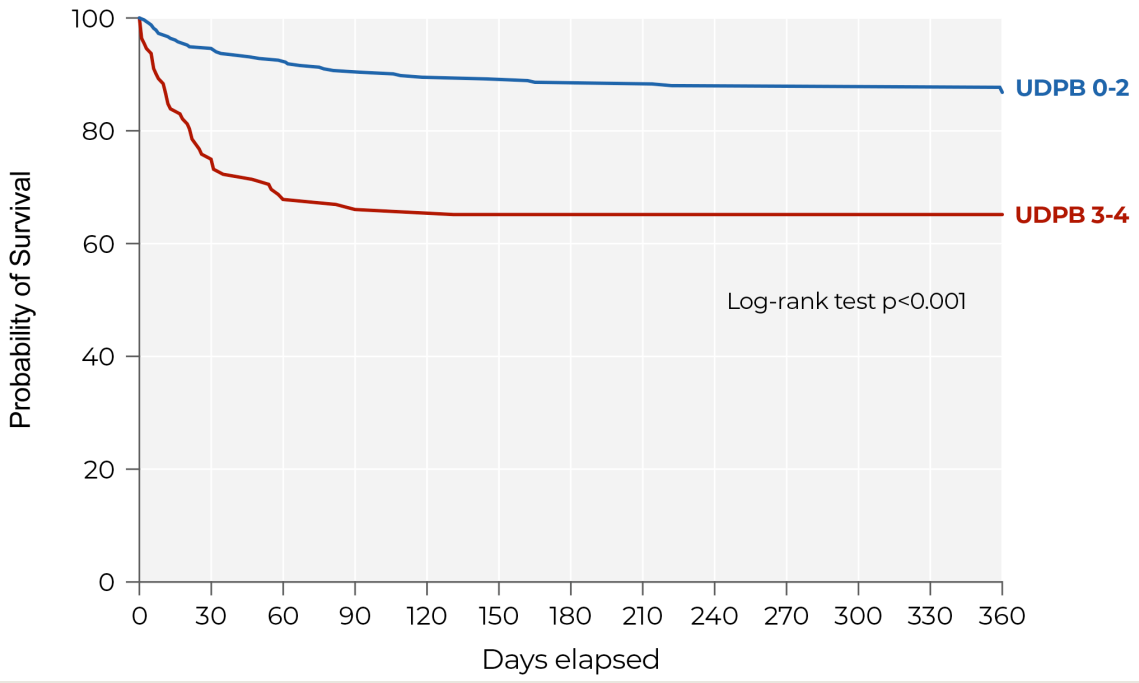

Fig. 2. One-year survival according to postoperative bleeding severity. Kaplan–Meier survival curves with log-rank test were used to compare survival according to Universal Definition of Perioperative Bleeding (UDPB) classification.

associated with shear-mediated platelet function defects and acquired von Willebrand syndrome.[44] Finally, the MCS implantation process itself can induce intrathoracic adhesions, complicating subsequent heart transplantation surgery.[45] Recent evidence suggests that MCS patients require more transfusions than non-MCS patients,

correlating with significant differences in 1-yr mortality rates.[46] However, the influence of time interval between MCS implantation and transplantation on bleeding after heart transplantation remains unknown.[47]

Our study shows that severe postoperative bleeding was associated with postoperative mortality in adjusted analyses and with major morbidity in exploratory unadjusted analyses, including PGD and acute kidney injury requiring renal replacement therapy. It is, of course, extremely difficult to distinguish between the direct effects of bleeding, the impacts of allogeneic transfusions, and the associated organ failures. Accounting for all these competitive risks in a time-dependent manner is virtually impossible. Nevertheless, the direct effect of allogeneic transfusion is an interesting mechanistic hypothesis. Subramaniam *et al.* reported significant correlation between allogeneic transfusions and a composite outcome of adverse events after heart transplantation, with an increase of 17% and 7%, respectively, for red blood cell and FFP transfusion.[20] In addition, red blood cell transfusion was associated with severe PGD and acute kidney failure. The higher incidences of PGD might be partially attributed to transfusion-related immunomodulation.[48] A national study conducted in the United Kingdom evaluating PGD risk factors also reported an association between PGD and blood product use.[49] In addition, a study of pediatric heart transplant recipients showed an increase in postoperative morbidity (sepsis, organ dysfunction, and the use of inotropes, as well as PGD) in a transfusion-dependent manner.[50] Our study also demonstrates a potential impact of severe bleeding on mortality up to 1 yr after heart transplantation. This association aligns with the scant literature available on the topic.[19,20]

As of now, specific recommendations for the perioperative management of patients undergoing heart transplantation cannot rely on robust data regarding the management of bleeding, hemostasis, and transfusion.[11,51] In the absence of specific data and guidelines, perioperative hemostasis and transfusion management in cardiac transplantations should likely adhere to current guidelines for cardiac surgery. This encompasses strategies such as preoperative optimization, management of anticoagulant and antiplatelet treatments, intraoperative blood conservation, judicious use of postoperative transfusions, and optimization of CPB.

Our study has several strengths. It reports data on severe bleeding complications after heart transplantation in a large cohort in two tertiary referral centers, using the validated UDPB classification. Preoperative variables and postoperative outcomes were clearly defined, and all consecutive cardiac transplant patients during a 7-yr period were included, thereby limiting selection bias. Comprehensive data on intra- and postoperative transfusions, comorbidities, and postoperative complications were collected with minimal missingness. Finally, a transparent prespecified statistical approach was applied to reduce confounding.

However, this study has notable limitations. First, the observational nature of this study allows interpretation of associations only and does not permit conclusions about underlying mechanisms. Second, despite the use of a robust statistical approach, residual confounding by unmeasured factors cannot be excluded. Third, because the analysis relied on medical records, information bias is possible. Fourth, the use of inhaled nitric oxide for right ventricular failure, a potential bleeding risk factor, was not systematically recorded. Fifth, although the cohort was substantial, the sample size did not allow assessment of changes in transfusion or hemostatic management practices (such as HMS, viscoelastic testing, and transfusion thresholds) over time. Finally, these findings likely reflect institutional and national practices in donor selection and intraoperative and early postoperative management, which may limit the generalizability of the results.

This study reports a high incidence of severe hemorrhagic complications after heart transplantation, particularly in patients with mechanical circulatory support, preoperative anemia, and long duration of CPB. These complications were associated with a significant increased morbidity and mortality. Larger studies are needed to better identify high-risk patients and to evaluate targeted prevention strategies.

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Competing Interests

Dr. Mansour received payments made to his institution from i-SEP (Nantes, France) for consulting fees, and from LFB (Les Ulis, France), Aguettant (Lyon France), Viatris (Lyon, France), and Pfizer (Paris, France) for lecture fees. The other authors declare no competing interests.

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Supplemental Digital Content

Supplemental Tables and Figures, https://links.lww.com/ALN/E386

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