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Outcomes With Heparin-Induced Thrombocytopenia After Cardiac Surgery

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Background. **Heparin-induced thrombocytopenia (HIT) is an immune-mediated reaction to heparin that provokes a prothrombotic state and causes a decline in platelet count. Data describing outcomes of HIT after cardiac surgery are limited. This study sought to determine the impact of HIT on short-term outcomes after cardiac surgery.**

Methods. **This was an observational study of cardiac surgeries from 2010 to 2018. Patients with HIT were matched against patients without HIT using 2:1 nearest-neighbor propensity matching. Matching was performed to assess the impact of HIT on operative mortality (The Society of Thoracic Surgeons definition) and thromboembolic events (including deep vein thrombosis, pulmonary embolism, stroke, and/or acute limb ischemia), which were the primary outcomes of interest.**

Results. **Of 11,820 patients undergoing a Society of Thoracic Surgeons indexed cardiac surgery, 131 (1.1%) developed HIT after their index operation. After matching operative mortality was 21.8% in HIT patients compared with 5.3% in non-HIT patients. Thromboembolic events occurred in 29.1% of HIT patients compared with 2.9% in non-HIT patients. On subanalysis operative mortality was significantly higher for the HIT group without thromboembolic events (16.7%) and the HIT group with thromboembolic events (34.4%) compared with the non-HIT group (5.3%). However operative mortality was not significantly higher in the HIT group with thromboembolic events compared with the HIT group without thromboembolic events, after Bonferroni correction.**

Conclusions. **Although uncommon, HIT is a highly morbid and potentially lethal complication, which should reinforce the importance of timely recognition and treatment of this adverse outcome.**

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated reaction to heparin that provokes a prothrombotic state and causes a decline in platelet count (usually 5-10 days after heparin exposure).[1-3] Because cardiac surgery involves administration of high-dose heparin during the operative proceedings, cardiac surgery patients are particularly at risk for the development of HIT.[1-3] Reportedly HIT may develop in 1% to 3% of cardiac surgery patients.[2] However not all thrombocytopenia is HIT. Thrombocytopenia after cardiac surgery may be due to hemodilution or consumption during cardiopulmonary bypass; however when thrombocytopenia occurs 5 to 10 days after the initial heparin exposure or is accompanied by a new thromboembolic event, HIT becomes highly suspicious. When IgG antibodies bind to platelet factor 4 (PF4), which are heparin complexes on the surface of platelets, there may be in situ platelet activation and/or platelet destruction by the reticuloendothelial system. However HIT often paradoxically presents with a thromboembolic event in the absence of clinical signs of severe thrombocytopenia (eg, petechial bleeding).

The 4T scoring system, which accounts for the relative decline in platelet count, the timing of thrombocytopenia, the development (or not) of thromboembolic events, and the likelihood of alternative etiologies for thrombocytopenia, defines the pretest probability for HIT positivity.[2] For patients with intermediate risk of HIT by the 4Ts (ie, $\geq$4 points), serologic testing should be initiated. Heparin antibody immunoassays can be used as a screening tool, given its high

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negative predictive value but low positive predictive value.[2] To confirm, the gold standard laboratory tests are heparin-induced platelet activation or serotonin release assays.[2]

Prior studies suggest that HIT is associated with significant morbidity and mortality, especially in the setting of major surgery.[2] However data describing outcomes of HIT after cardiac surgery are limited and conflicting and are derived from studies with heterogeneous design.[4-8] Moreover some studies report that in-hospital mortality for HIT is as high as 33%, whereas other studies have reported in-hospital mortality to be as low as 1%.[6,9] Nevertheless HIT has been associated with greater healthcare cost and utilization.[7,10] As such, HIT remains an important complication after cardiac surgery and may represent an area for quality improvement.

This study sought to determine the impact of HIT on short-term postoperative outcomes in a large, contemporaneous cohort of cardiac surgery patients at a single institution. We hypothesized that the development of postoperative HIT will be associated with worse operative mortality (in-hospital and/or 30-day mortality) and increased postoperative morbidity and resource use after cardiac surgery.

Patients and Methods

Patient Population and Study Design

This was an observational study using a prospectively maintained institutional database of all consecutive cardiac surgeries performed at the University of Pittsburgh Medical Center between 2010 and 2018. Definitions and terminology were consistent with The Society of Thoracic Surgeons (STS) database. This study was approved by the Institutional Review Board of the University of Pittsburgh.

Index cardiac surgeries included for analysis were isolated coronary artery bypass grafting, isolated aortic valve replacement, isolated mitral valve replacement, coronary artery bypass grafting + aortic valve replacement, coronary artery bypass grafting + mitral valve replacement, isolated mitral valve repair, and coronary artery bypass grafting + mitral valve repair. In addition to elective cases, urgent and emergent cases were also included.

For this cohort of patients postoperative HIT status was determined with the institutional dataset. HIT was defined as a clinical-pathologic syndrome, determined by a positive anti-PF4–heparin antibody screen, along with a confirmatory heparin-induced platelet activation assay in the setting of thrombocytopenia or a new thromboembolic event. The charts of all patients with HIT positivity and thromboembolic complications were reviewed to determine if HIT developed *after* heparin administration in the setting of acute-onset postoperative thromboembolic complications, such as deep vein thrombosis (DVT)/pulmonary embolism (PE). HIT was promptly treated by discontinuing heparin-containing agents and initiating argatroban or lepirudin as an alternative anticoagulant. Because previous studies suggest that reexposure to heparin in patients with prior HIT does not increase the risk for subsequent HIT,[1-3,11] patients with history of HIT were not excluded from analysis.

Finally this institution does not routinely test for preoperative HIT antibodies or perform heparin-induced platelet activation assay or serotonin release assays before cardiac surgeries. The primary aims of this study were to assess the impact of developing postoperative HIT on operative mortality (STS definition) and the occurrence of any thromboembolic event, inclusive of DVT, PE, stroke, and/or acute limb ischemia.

Statistical Methods and Analysis

Primary stratification was between the HIT-positive group and the non-HIT group. Distributional characteristics for variables were checked for normalcy. Continuous variables were presented as mean ± SD for normally distributed data or median and interquartile range for nonnormally distributed data. Categorical data were summarized using frequency and percentage. The Student *t* test was used to compare normally distributed continuous variables between groups, whereas the χ^2 test was used to compare categorical variables between groups, as appropriate. All tests were 2-sided with an alpha level of 0.05 considered to indicate statistical significance.

Differences between the HIT-positive group and the non-HIT group were described for baseline demographic, clinical, and operative variables. To reduce selection bias patients were propensity matched for HIT status. Logistic regression was used to calculate propensity scores based on age, sex, diabetes mellitus, chronic dialysis use, hypertension, chronic lung disease, peripheral vascular disease, cerebrovascular disease, preoperative platelet count, congestive heart failure, ejection fraction, redo cardiac surgery, STS predicted risk of mortality, surgical urgency, and type of index cardiac surgery. These variables were included in the algorithm because they have either been associated with the development of HIT or have been associated with operative mortality.

The matched cohort was generated using 2:1 nearest-neighbor matching with a caliper of 0.2 of the SD of the logit propensity score. After matching standardized mean differences were calculated to assess covariate balance, with <10% considered balanced. After propensity matching univariable differences in short-term postoperative outcomes were descriptively analyzed across HIT status. Operative mortality followed the STS definition, which includes 30-day mortality and in-hospital mortality (regardless of time from operation). Finally for the propensity-matched cohort operative mortality was assessed across 3 separate subgroups: patients without HIT, patients who developed HIT without thromboembolic events, and patients who developed HIT along with a thromboembolic event. Thromboembolic events were analyzed as a composite outcome, inclusive of DVT, PE, stroke, and/or acute limb ischemia. For this secondary subgroup analysis operative mortality was assessed with the χ^2 test using the Bonferroni correction for multiple comparisons, with a threshold $P = .017$ accounting for

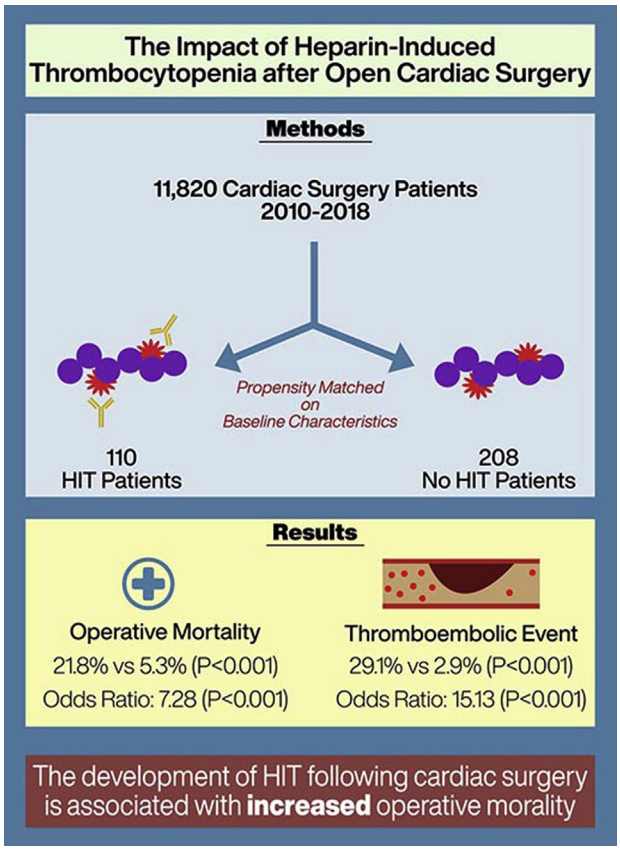

Figure 1. Postoperative heparin-induced thrombocytopenia (HIT) was associated with increased operative mortality and thromboembolic events after cardiac surgery.

three comparisons (0.05/3). All statistical analyses were performed using STATA, version 15.0 (StataCorp, College Station, TX).

Results

Baseline Demographic, Clinical, and Operative Variables

Of an identified 11,820 patients undergoing an STS indexed cardiac surgery, 131 patients (1.1%) developed HIT after their index operation and 11,689 (98.9%) did not. Supplemental Table 1 lists the baseline characteristics for the entire cohort (N = 11,820) analyzed by HIT status. A 2:1 nearest-neighbor propensity matching yielded 110 patients with HIT and 208 patients without HIT. Table 1 presents demographic, clinical, and operative data for the matched cohort (n = 318) analyzed by HIT status. After matching, certain variables remained imbalanced across groups (standardized mean difference > 10%), with the HIT group being younger (68.6 ± 10.9 vs 69.6 ± 10.7 years), more likely to have cerebrovascular disease (22.7% vs 16.8%), and more likely to have lower ejection fraction (45.9 ± 16.1 vs 47.3 ± 15.2) than the non-HIT group. The groups were otherwise balanced across all baseline covariates (standardized mean difference < 10%).

Postoperative Outcomes

Supplemental Table 2 presents short-term postoperative outcomes across HIT status for the entire unmatched cohort (N = 11,820), and Table 2 presents these outcomes for the propensity matched cohort (n = 318). The HIT group had higher operative mortality (21.8% vs 5.3%), with longer length of intensive care unit stay (302.1 ± 325.8 vs 86.8 ± 120.9 hours) and longer length of total hospital stay (27.1 ± 15.6 vs 12.4 ± 8.8 days) than the non-HIT group. The HIT group had more thromboembolic events (29.1% vs 2.9%) than the non-HIT group, which included more DVT and/or PE (6.4% vs 0.0%), more stroke (7.3% vs 2.4%), and more acute limb ischemia (18.2% vs 0.5%) (Figure 1). None of the patients with thromboembolic events and HIT developed HIT *after* being anticoagulated for a postoperative thromboembolic complication. The HIT group was more likely to have prolonged mechanical ventilation (>24 hours, 62.7% vs 16.4%), more likely to develop sepsis (17.3% vs 1.0%), more likely to develop new-onset atrial fibrillation (62.7% vs 35.1%), and more likely to have a new dialysis requirement (30.9% vs 4.3%) than the non-HIT group, but rates of reexploration for bleeding were similar across each group ($P = .253$). The HIT group was more likely to receive postoperative blood products (81.8% vs 42.8%) than the non-HIT group, with more units of packed red blood cells transfused (6.3 ± 6.7 vs 2.6 ± 2.3) and more units of fresh frozen plasma transfused (6.0 ± 5.4 vs 2.6 ± 1.7) but with similar amounts of cryoprecipitate ($P = .140$) and platelet transfusion ($P = .178$). Finally cardiopulmonary bypass and ischemic times were similar across each group ($P > .05$)

Finally the HIT group was split into 2 groups, those with and without thromboembolic events, and compared against the non-HIT group. For the non-HIT group operative mortality was 5.3% (11/208), for the HIT group without thromboembolic events operative mortality was 16.7% (13/78), and for the HIT group with thromboembolic events operative mortality was 34.4% (11/32). When comparing operative mortality across these 3 groups, operative mortality was significantly different (χ^2 test, $P < .001$). Using the Bonferroni correction for 3 comparisons (0.05/3), a threshold $P = .017$ was necessary to achieve statistical significance for this subgroup comparison. Operative mortality was significantly higher for the HIT group without thromboembolic events (16.7%) compared with the non-HIT group (5.3%, $P = .002$). Operative mortality was significantly higher for the HIT group with thromboembolic events (34.4%) compared with the non-HIT group (5.3%, $P < .001$). However operative mortality was not significantly higher in the HIT group with thromboembolic events (34.4%) compared with the HIT group without thromboembolic events (16.7%, $P = .041$), given Bonferroni correction.

Comment

Although uncommon, HIT is a highly morbid and potentially lethal complication after heparin exposure,

Table 1. Baseline Characteristics Comparing Non-HIT Patients With HIT Patients After Propensity Score Matching

Variable	Non-HIT Group (n = 208)	HIT Group (n = 110)	Standardized Mean Difference[a]
Age, y	69.6 ± 10.7	68.6 ± 10.9	–0.121
Sex, female	87 (41.8)	44 (40.0)	–0.019
White race	192 (92.3)	103 (93.6)	0.037
Body mass index, kg/m^2	30.5 ± 7.0	30.6 ± 6.7	0.048
Diabetes mellitus	117 (56.3)	60 (54.6)	–0.018
Chronic dialysis use	19 (9.1)	11 (10.0)	0.000
Hypertension	185 (88.9)	98 (89.1)	0.000
Chronic lung disease	69 (33.2)	34 (30.9)	–0.052
Peripheral vascular disease	39 (18.8)	21 (19.1)	–0.023
Cerebrovascular disease	35 (16.8)	25 (22.7)	0.151
Preoperative hematocrit	36.9 ± 5.8	36.6 ± 5.4	–0.023
Preoperative platelet count, $\times 10^9$/L	199.0 ± 68.0	195.7 ± 65.5	–0.032
Preoperative creatinine, mg/dL	1.52 ± 1.88	1.66 ± 2.06	0.052
Atrial fibrillation or atrial flutter	49 (23.6)	25 (22.7)	–0.047
Previous myocardial infarction	120 (57.7)	67 (60.9)	0.073
Congestive heart failure	100 (48.1)	50 (45.5)	–0.078
Ejection fraction	47.3 ± 15.2	45.9 ± 16.1	–0.101
Redo cardiac surgery	17 (8.2)	7 (6.4)	–0.088
Society of Thoracic Surgeons predicted risk of mortality	7.8 ± 11.7	7.7 ± 11.4	–0.083
Surgical status			0.074
Elective	60 (28.9)	35 (31.8)	
Urgent	135 (64.9)	59 (53.6)	
Emergent/salvage	13 (6.3)	16 (14.6)	
Surgical procedure			–0.046
Isolated coronary artery bypass graft	100 (48.1)	53 (48.2)	
Isolated valve	52 (25.0)	27 (24.6)	
Coronary artery bypass graft + single valve	56 (26.9)	30 (27.3)	

[a]Standardized mean difference assesses balance after matching, with <10% considered balanced.

Values are mean ± SD or n (%).

HIT, heparin-induced thrombocytopenia.

especially in the setting of major surgery. Given the routine administration of high-dose heparin for intraoperative anticoagulation, cardiac surgery patients are particularly at risk for the development of this significant complication. However data describing outcomes of HIT after cardiac surgery are limited and conflicting; therefore we undertook this large, single-institutional series to examine the impact of HIT after cardiac surgery. Although uncommon, the postoperative development of HIT was associated with a host of adverse outcomes. After propensity matching HIT remained significantly associated with operative mortality and the occurrence of thromboembolic events, which highlights the importance of having a high index of suspicion for HIT and promptly switching heparin to an alternative anticoagulation when it is diagnosed.

Prior reports indicate that the incidence of HIT ranges from 0.3% to 2.8% among cardiac surgery patients.[4-8] In this study the incidence was 1.1%, which conforms with these prior estimates. Numerous risk factors have been identified for the development of HIT, most notably female sex, the pathophysiology of which has not yet been elucidated.[4,7,12] However other identified risk factors are chronic renal failure, congestive heart failure, atrial fibrillation, and chronic obstructive pulmonary disease.[4,7] In line with prior studies HIT patients in this study's unmatched cohort were more likely to be female and to have chronic dialysis use, chronic lung disease, atrial fibrillation or flutter, and congestive heart failure. It is possible that in virtue of these comorbidities, these patients may have had recent heparin exposure before their index cardiac operation, thereby placing them at increased risk for developing HIT through prior potentiation of their immune-mediated response to heparin. However this hypothesis is unable to be verified, given the lack of preoperative heparin exposure data in the present study. Moreover the HIT group for this study's unmatched cohort was more likely to undergo higher complexity cardiac operations with longer cardiopulmonary bypass time and ischemic time. It is possible that these patients experience more perioperative inflammation, which has been associated with increased risk for developing HIT, a relationship

Table 2. Perioperative Outcomes Comparing Non-HIT Patients With HIT Patients After Propensity Score Matching

Variable	Non-HIT Group (n = 208)	HIT Group (n = 110)	P[a]
Operative mortality (Society of Thoracic Surgeons definition)	11 (5.3)	24 (21.8)	<.001
Intensive care unit length of stay, h	86.8 ± 120.9	302.1 ± 325.8	<.001
Total length of hospital stay, days	12.4 ± 8.8	27.1 ± 15.6	<.001
Any thromboembolic event[b]	6 (2.9)	32 (29.1)	<.001
Deep vein thrombosis and/or pulmonary embolism	0 (0.0)	7 (6.4)	<.001
Stroke	5 (2.4)	8 (7.3)	.037
Acute limb ischemia	1 (0.5)	20 (18.2)	<.001
Prolonged ventilation (>24 h)	34 (16.4)	69 (62.7)	<.001
Sepsis	2 (1.0)	19 (17.3)	<.001
New-onset atrial fibrillation	73 (35.1)	69 (62.7)	<.001
New dialysis requirement	9 (4.3)	34 (30.9)	<.001
Reexploration for bleeding	6 (2.9)	6 (5.5)	.253
Postoperative blood product requirement (yes or no)	89 (42.8)	90 (81.8)	<.001
Packed red blood cells, no. of units	2.6 ± 2.3	6.3 ± 6.7	<.001
Fresh frozen plasma, no. of units	2.6 ± 1.7	6.0 ± 5.4	.012
Cryoprecipitate, no. of units	1.1 ± 0.3	1.7 ± 1.1	.140
Platelets, no. of units	1.7 ± 1.1	2.9 ± 3.9	.178
Cardiopulmonary bypass time, min	117.5 ± 45.0	128.3 ± 63.6	.101
Ischemic time, min	89.5 ± 39.8	92.6 ± 47.2	.570

[a]For continuous variables *P* values were calculated by the Student *t* test. For categorical variables *P* values were calculated by the χ^2test; [b]Includes deep vein thrombosis, pulmonary embolism, stroke, and/or acute limb ischemia.

Values are mean ± SD or n (%).

HIT, heparin-induced thrombocytopenia.

that is potentially mediated by increased serum levels of interleukin-6.[13] As such reducing perioperative inflammation may represent an opportunity for limiting the incidence of HIT after cardiac surgery. Nevertheless the abovementioned risk factors should help physicians identify patients for whom they must have a high index of suspicion of developing HIT.

HIT may paradoxically lead to thrombocytopenic thrombosis, which is due to antibody-mediated platelet activation. In this study thromboembolic events occurred in nearly 30% of patients after propensity matching, making thromboembolic events over 10 times as prevalent in HIT patients compared with non-HIT patients. Thromboembolic events included DVT, PE, stroke, and acute limb ischemia, whereas the correlation of HIT with these events remained even after risk adjustment. Moreover HIT patients had increased rates of prolonged mechanical ventilation, sepsis, new-onset atrial fibrillation, and new dialysis requirement and longer intensive care unit stays and longer length of total hospital stays, after propensity matching. Admittedly these are unadjusted associations; however these adverse outcomes have been similarly reported in previous studies.[4-8] Nevertheless the higher proportion of postoperative morbidity among HIT patients, especially thromboembolic events, supports the idea that HIT constitutes a prothrombotic state with potentially devastating consequences for postoperative recovery. Finally it is interesting to note that rates of reexploration for bleeding were not significantly different across groups, suggesting that bleeding complications from argatroban or lepirudin anticoagulation were not markedly elevated in the HIT group.

Although some studies report that in-hospital mortality for HIT is as high as 33%, other studies have reported in-hospital mortality to be as low as 1%.[6,9] In this study operative mortality (STS definition) was 21.8% in HIT patients after propensity matching, which was significantly higher than the non-HIT group, an association that remained even after risk adjustment. It is likely that the increased operative mortality for HIT can be ascribed to the increased prevalence of thromboembolic events in the HIT group. DVT, PE, stroke, and acute limb ischemia are devastating complications that may adversely impact survival after cardiac surgery,[14-16] which highlights the importance of promptly discontinuing heparin and administering a nonheparin anticoagulant before intravascular thrombosis can occur. Indeed late recognition of postoperative HIT has been associated with worse outcomes than early recognition in cardiac surgery patients.[9] Of note however when comparing the HIT group without thromboembolic complications with the HIT group with thromboembolic complications, operative mortality was not significantly different after Bonferroni correction ($P = .041 > .017$). Although this nonsignificance may be due to sample size, this suggests that the worse overall mortality for developing HIT after cardiac surgery may not be entirely attributable to the development of thromboembolic complications.

These findings suggest the importance of timely, but cost-conscious, diagnosis and treatment of HIT.[17-20]

Previous studies that prospectively measured preoperative anti-PF4–heparin antibodies (of all immunoglobulin classes) found that detectable antibodies in the preoperative setting did not correlate with postoperative development of HIT or thromboembolic events.[17] Moreover previous studies suggested that reexposure to heparin in patients with prior HIT does not increase the risk for subsequent HIT.[1,11] Together these findings suggest that preoperative screening for anti-PF4–heparin antibodies is unnecessary for most patients. These findings have also led to the accepted clinical practice of using intraoperative heparin-based anticoagulation even for patients with a history of HIT.[21,22] In the postoperative setting previous research suggests that a large percentage of patients will develop antibodies to PF4–heparin complexes; however few of these seroconverted patients will ultimately develop clinically significant platelet activation. For instance Welsby and colleagues[5] found that seropositivity for PF4 antibodies was not associated with increased in-hospital mortality or thromboembolic events after cardiac surgery. This phenomenon is especially notable for cardiac surgery patients, among other noncardiac operations. For example Warkentin and associates[19] found that the prevalence of patients with heparin-dependent antibodies who did not develop HIT was higher for cardiac surgery than orthopedic surgery. Thus HIT should be defined as a clinical-pathologic syndrome, not simply serologically. By implication some have suggested that although routine screening for antibodies is not justified, thrombocytopenia and/or platelet counts that decline > 50% should trigger screening for PF4–heparin antibodies.[5,20] As such routine platelet count monitoring and trending is sufficient for detecting the initial development of HIT in the postoperative setting.[20] Finally given the sensitivities of the antibody screens negative testing should reassure against HIT, whereas heparin anticoagulation should be discontinued with a positive screen that is administered in the appropriate clinical setting.

Limitations

There are important limitations to this analysis. Compared with the non-HIT group patients with HIT had more underlying comorbidities; thus the conclusion that the development of HIT is associated with increased risk for operative mortality and postoperative thromboembolic events may be confounded by higher preoperative risk. Although propensity matching was used to overcome this discrepancy the magnitude of association of HIT with adverse postoperative outcomes may not be as profound as this study suggests. Furthermore certain data were unavailable for this institutional cohort, including heparin exposure before the index operation, total heparin dosage during the index admission, status of preoperative anti-PF4–heparin antibodies, history of prior HIT, and postoperative platelet counts for the entire cohort. Analysis of these variables would significantly contribute to diagnostic and clinical decision-making and thereby strengthen the findings of this study.

Conclusions

Despite these limitations this is a large, single-institutional series examining the impact of HIT after cardiac surgery. Although HIT only developed in 1.1% of patients in this cohort, operative mortality was 21.8% in HIT patients compared with 5.3% in non-HIT patients after patient matching. Similarly thromboembolic events (inclusive of DVT, PE, stroke, and/or acute limb ischemia) occurred in nearly 30% of HIT patients compared with 2.9% in non-HIT patients after patient matching. Thus although uncommon, HIT is an immune-mediated prothrombotic state that is a highly morbid and potentially lethal complication after cardiac surgery. These findings should reinforce the importance of timely recognition and treatment of this adverse postoperative outcome.

References

1. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia and cardiac surgery. *Ann Thorac Surg*. 2003;76:2121-2131.
2. Greinacher A. Heparin-induced thrombocytopenia. *N Engl J Med*. 2015;373:252-261.
3. Solanki J, Shenoy S, Downs E, Palkimas S, Goldman S, Sharma AM. Heparin-induced thrombocytopenia and cardiac surgery. *Semin Thorac Cardiovasc Surg*. 2019;31:335-344.
4. Seigerman M, Cavallaro P, Itagaki S, Chung I, Chikwe J. Incidence and outcomes of heparin-induced thrombocytopenia in patients undergoing cardiac surgery in North America: an analysis of the nationwide inpatient sample. *J Cardiothorac Vasc Anesth*. 2014;28:98-102.
5. Welsby IJ, Krakow EF, Heit JA, et al. The association of anti-platelet factor 4/heparin antibodies with early and delayed thromboembolism after cardiac surgery. *J Thromb Haemost*. 2017;15:57-65.
6. Arangalage D, Lepage L, Faille D, et al. Presentation, management and outcome of heparin-induced thrombocytopenia after valvular heart surgery. *Eur J Cardiothorac Surg*. 2016;50:1132-1138.
7. Aguayo E, Sanaiha Y, Seo YJ, et al. Heparin-induced thrombocytopenia in cardiac surgery: incidence, costs, and duration of stay. *Surgery*. 2018;164:1377-1381.
8. Kerendi F, Thourani VH, Puskas JD, et al. Impact of heparin-induced thrombocytopenia on postoperative outcomes after cardiac surgery. *Ann Thorac Surg*. 2007;84:1548-1555.
9. Walls JT, Curtis JJ, Silver D, et al. Heparin-induced thrombocytopenia in open heart surgical patients: sequelae of late recognition. *Ann Thorac Surg*. 1992;53:787-791.
10. Aranda-Michel E, Bianco V, Sultan I, Gleason TG, Navid F, Kilic A. Predictors of increased costs following index adult cardiac operations: insights from a statewide publicly reported registry. *J Card Surg*. 2019;34:708-713.
11. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med*. 2001;344:1286-1292.
12. Huckaby LV, Seese LM, Sultan I, et al. The impact of sex on outcomes after revascularization for multivessel coronary disease. *Ann Thorac Surg*. 2020;110:1243-1250.
13. Paparella D, Scrascia G, Galeone A, et al. Formation of anti-platelet factor 4/heparin antibodies after cardiac surgery: influence of perioperative platelet activation, the inflammatory response, and histocompatibility leukocyte antigen status. *J Thorac Cardiovasc Surg*. 2008;136:1456-1463.
14. Seese L, Sultan I, Gleason TG, et al. The impact of major postoperative complications on long-term survival after cardiac surgery. *Ann Thorac Surg*. 2020;110:128-135.

15. Sultan I, Bianco V, Kilic A, et al. Predictors and outcomes of ischemic stroke after cardiac surgery. *Ann Thorac Surg*. 2020;110:448-456.
16. Josa M, Siouffi SY, Silverman AB, Barsamian EM, Khuri SF, Sharma GV. Pulmonary embolism after cardiac surgery. *J Am Coll Cardiol*. 1993;21:990-996.
17. Selleng S, Malowsky B, Itterman T, et al. Incidence and clinical relevance of anti-platelet factor 4/heparin antibodies before cardiac surgery. *Am Heart J*. 2010;160:362-369.
18. Everett BM, Yeh R, Foo SY, et al. Prevalence of heparin/platelet factor 4 antibodies before and after cardiac surgery. *Ann Thorac Surg*. 2007;83:592-597.
19. Warkentin TE, Sheppard JA, Horsewood P, et al. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96:1703-1708.
20. Gruel Y, Pouplard C. Post-operative platelet count profile: the most reliable tool for identifying patients with true heparin-induced thrombocytopenia after cardiac surgery. *J Thromb Haemost*. 2010;8:27-29.
21. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2015;148:1529.
22. Shore-Lesserson L, Baker RA, Ferraris VA, et al. The Society of Thoracic Surgeons, the Society of Cardiovascular Anesthesiologists, and the American Society of ExtraCorporeal Technology: clinical practice guidelines-anticoagulation during cardiopulmonary bypass. *Ann Thorac Surg*. 2018;105:650-662.