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ORIGINAL ARTICLE

Heparin-induced thrombocytopenia after cardiac surgery. A single-center, retrospective cohort study

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Abstract

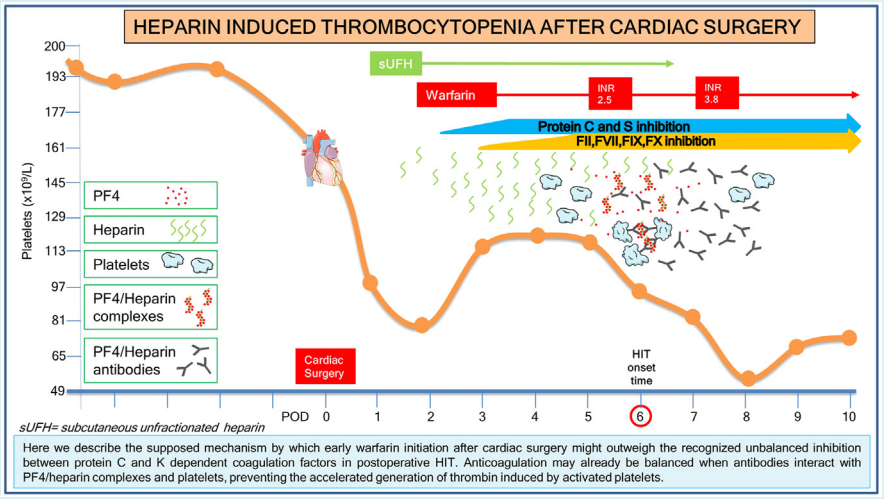
Background: Cardiac surgery is a high-risk setting for heparin-induced thrombocytopenia (HIT). However, large differences in its incidence, rate of thrombotic complications, and mortality have been reported in this context. Few studies address the pharmacologic management of HIT specifically in this setting.

Objectives: To describe the incidence, outcomes, and management of patients with HIT in our cohort and to compare them with patients presenting platelet factor 4/heparin antibodies but without platelet-activating capacity.

Methods: A retrospective observational study was conducted over a period of 10 years and 6 months on 13,178 cardiac operations in a single high-volume cardiac surgery center.

Results: HIT was diagnosed in 0.22% of patients. HIT with associated thromboembolic complications occurred in 0.04% of cases. Two deaths at 30 days were registered, both in patients with associated thrombosis. The 4T score showed a 99.9% negative predictive value. The immunoglobulin G-specific chemiluminescence test positivity rate was highly predictive of HIT. Warfarin was often started early after surgery, and although it was rarely stopped when the diagnosis of HIT was made, no new thromboembolic complications subsequently occurred. Thrombocytopenia appeared to be a poor prognostic sign, whatever the cause.

Conclusion: Although rare, HIT is characterized by high mortality in this setting, especially if thrombotic complications occur. Large multicentric studies or an international registry should be created to enhance the scientific evidence on HIT diagnosis and management in this context.



KEYWORDS
heparin, platelet factor 4, thoracic surgery, thrombocytopenia, warfarin

Essentials

- Cardiac surgery is a high-risk setting for heparin-induced thrombocytopenia (HIT).
- We showed 0.22% HIT and 0.04% HIT with thrombosis incidence with a 6.9% cumulative mortality.
- Warfarin can precipitate thrombosis in patients with circulating HIT antibodies.
- When warfarin was initiated well before HIT diagnosis and maintained, no thrombosis occurred.

1 | INTRODUCTION

Heparin-induced thrombocytopenia (type 2 HIT) is a life-threatening condition in which antibodies directed against the heparin-platelet factor 4 complex (PF4/H-ab) cause thrombocytopenia, platelet (PLT) activation, and even HIT with thrombosis (HITT) [1].

Cardiac surgery is considered a high-risk setting for HIT. Cardiac surgery patients undergo extensive heparin treatment during their perioperative course, and they need full heparin anticoagulation during surgery, regardless of the type of procedure and the need for cardiopulmonary bypass (CPB).

Moreover, the diagnosis of HIT may be challenging in this setting: transient thrombocytopenia is common after cardiac surgery, as it can be induced by heparin itself (type 1 HIT), surgery, CPB, other drugs, or other causes.

Furthermore, nonspecific and clinically insignificant PF4/H-ab are often detectable, even in patients who do not present the clinical picture of type 2 HIT [2].

Therefore, the diagnosis is based on clinical suspicion, corroborated by the 4T risk score, combined with laboratory detection of PF4/H-ab [3]. The presence of PF4/H-ab is detected with an immunologic assay, but even when present, the diagnosis must be confirmed by a functional test demonstrating their ability to cause *in vitro* PLT activation induced by heparin [4]. The incidence of HIT in the cardiac surgery setting has been reported to be 0.2% to 3%, with major differences among various studies [5,6].

The objective of this analysis was to describe HIT incidence, complications, management, and cumulative mortality in patients undergoing consecutive cardiac operations during a 10-year and 6-month interval in a single-center, large-volume cardiac surgery unit. In addition, patients with HIT confirmed by functional testing were compared with patients who tested positive for PF4/H-specific immunoglobulin (Ig)G antibodies but without PLT-activating capacity.

2 | METHODS

2.1 | Study design

We performed a retrospective observational single-center cohort study (Cardiac Surgery Unit of a teaching hospital, Department of Cardiothoracic and Vascular Surgery, Azienda Ospedaliero Universitaria Careggi) between February 2013 and August 2023. This study was approved by the Institutional Review Board, which waived the requirement for written informed consent from the participants (register number: CE23039). This manuscript was prepared in accordance with principles set forth in the Helsinki Declaration [7] and the Strengthening the Reporting of Observational Studies in Epidemiology statement [8].

2.2 | Patient selection

We reviewed the electronic medical records of all consecutive patients who underwent cardiac surgery during the study period. Inclusion criteria were age ≥18 years, major cardiac surgery (both on-CPB or off-pump), and use of unfractionated heparin (UFH) for anticoagulation during the procedure. The total number of patients who underwent major cardiac surgery (TNCS) and fit the inclusion criteria was recorded. From the laboratory database, all the patients who were investigated for PF4/H-ab were extracted and included in the study. The index date was the date of surgery, and the duration of follow-up was 30 days from the index date.

2.3 | Perioperative anticoagulation management protocol

All the patients included in the study received intravenous UFH to achieve the target-activated clotting time (ACT). Target ACT was 480 seconds when CPB was used and 300 seconds for off-pump procedures. A heparin dose between 150 and 400 UI/kg was usually administered to achieve these ACT values. At the end of surgery, protamine sulfate was administered to neutralize heparin in a ratio of 10 mg/1000 IU of UFH.

In patients who required postoperative therapeutic anticoagulation (valve repair or replacement, continuous renal replacement therapy [CRRT], intra-aortic balloon pump [IABP], or patients at high thrombotic risk), continuous infusion of intravenous UFH was administered to achieve a target-activated partial thromboplastin time of 1.5 to 2 times the normal range until warfarin was imbricated if required (eg, valvular surgery). Warfarin, where appropriate, was usually started on postoperative day (POD) 2 if bleeding was absent. In all the patients, subcutaneous UFH 5000 IU was administered 2 or 3 times a day for venous thromboembolism prophylaxis starting from POD 1 unless contraindicated and until warfarin stable anticoagulation was achieved.

2.4 | Serological assays

PF4/H-ab was investigated through IgG-specific anti-PF4–heparin chemiluminescent assay (CLIA) [9]. This test was performed if the 4T score was ≥4 or at discretion of the attending physician and hematologist for patients scoring <4. If CLIA tested positive (≥1 U/mL), a functional assay test was performed. The presence of HIT was defined by a positive washed-PLT functional assay: the heparin-induced PLT activation assay (HIPA) [4].

2.5 | Study protocol

The total number of patients who underwent cardiac surgery and who met the inclusion criteria was extracted from our institutional electronic database. The surgical case mix and the overall 30-day cumulative mortality of the TNCS in the study period were evaluated.

Patients belonging to this cohort who were prescribed CLIA/HIPA tests were extracted from the laboratory database and divided into 3 groups based on test results:

- CLIA-negative group,
- HIPA-negative group (CLIA positive and HIPA negative), and
- HIT group (CLIA positive and HIPA positive).

The last 2 groups were compared.

2.6 | Data collection

Study data were collected and managed using REDCap electronic data capture tools hosted at Azienda Ospedaliero Universitaria Careggi Firenze [10]. The following variables were noted: age, biological sex, cardiovascular risk factors, peak PLT count, PLT count nadir, percent reduction of PLTs, thrombocytopenia onset time, type of cardiac surgery, and CPB use. The 4T score of CLIA-positive patients was calculated from the clinical records [11]. The patterns of PLT reduction after the operation were also classified as follows (Supplementary Figure):

- pattern A, or typical onset profile, usually biphasic, where PLT count dropped right after surgery, then recovered in the next 72 hours, and decreased again between PODs 5 and 10.
- pattern B, or rapid onset profile, where thrombocytopenia occurred immediately after CPB but persisted or worsened beyond POD 4 [12].

The peak PLT count, the PLT nadir, and the PLT percent change were assessed differently depending on the presentation pattern type. The peak PLT value was the highest postoperative PLT value after recovery in pattern A, which occurred just before the beginning of the second downslope, whereas in pattern B, it was the PLT count registered before the admission to the operating room. The onset time of thrombocytopenia, as well as any other event, was registered referring to the day of surgery that was included in the count as day 0. However, for 4T score calculation, the effective onset time of thrombocytopenia was calculated starting from the first day of patient's exposure to heparin if the drug was started before surgery. PLT count nadir was defined as the lowest PLT count registered after the peak PLT count. Percent change in PLT count was calculated as (peak PLT − PLT nadir)/peak PLT × 100 (Supplementary Figure).

Incidence of suspected HIT was calculated as number of patients in which a CLIA test was performed/TNCS × 100. Incidence of HIT was calculated as number of HIPA-positive patients/TNCS × 100. The incidence of HITT was calculated as number of patients with HIT with associated thromboembolic complications/TNCS × 100.

Primary outcomes were 30-day cumulative mortality and any type of arterial or venous thromboembolic complication that occurred in the postoperative period during the hospital stay and the study period.

Bilateral lower-extremity compression ultrasonography was performed in all the patients in whom HIT was suspected by screening for asymptomatic vein thrombosis, according to current guidelines.

Secondary endpoints were the occurrence of postoperative acute kidney injury (AKI), need for CRRT, sepsis, and inotropic or mechanical cardiac support (IABP and extracorporeal cardiac life support). Inotropic support was defined as the use of dopamine ≥ 5 μg/kg/min, norepinephrine ≥ 0.1 μg/kg/min, or any dose of epinephrine, dobutamine, or levosimendan. Sepsis was defined based on the Sepsis-3 criteria [13]. Hospital length of stay (LOS) was also registered. AKI was evaluated by calculating the percent change in serum creatinine from baseline and was defined as an increase of serum creatinine ≥ 1.5 times baseline according to the Kidney Disease: Improving Global Outcomes guidelines [14].

Data on the pharmacologic management of suspected and confirmed cases were also collected.

Statistical analysis

The variables examined in the HIT- and HIPA-negative groups reported 0% to 2% missing data, except for body mass index (BMI, 25%). A Shapiro–Wilk test ($P > .05$) and a visual inspection of their histograms, normal q–q plots, and box plots were used to assess the normality of the data distribution. Data are expressed as means (SD) or medians (IQR) as appropriate. A Levine's test verified the equality of variances in the normally distributed variables (homogeneity of variance if $P < .05$); otherwise, the Mann–Whitney U-test was used to determine differences between groups. The chi-squared test or Fisher's exact test was applied to categorical variables where appropriate. The threshold for statistical significance was set at $P < .05$. Receiver operating characteristic (ROC) curves for 4T score and CLIA test results were also computed. These were calculated to assess sensitivity and specificity in detecting a positive HIPA value. Area under the ROC curve (AUC) with the 95% CI and Youden's index, sensitivity, specificity, the best cutoff at the highest Youden index, and its positive and negative predictive value (NPV) were calculated for each parameter. The overall test performance, assessed by AUC, was graded based on the traditional point system (0.5-0.6: fail; 0.6-0.7: poor; 0.70-0.80: fair; 0.80-0.90: good; and 0.90-1.00: excellent). Statistical analysis was performed with SPSS 22.0 (IBM, SPSS Inc) software.

3 | RESULTS

Analyses with complete cases and cases with some missing data on the items showed no statistically significant difference. Therefore, imputation of missing data was not performed.

3.1 | Patient population

A total of 13,178 consecutive patients underwent major heart surgery between February 2013 and August 2023. Of these, 2207 were off-pump coronary artery bypass graft operations (OPCABG), and 10,971 patients were operated on-CPB. The overall case mix, together with that of the suspected cases who tested negative for CLIA or HIPA tests and that of confirmed HIT group (HIPA positive), is detailed in Table 1. Patients' demographics, comorbidities, and cardiovascular risk factors of HIPA-negative and HIT patients are shown in Table 2.

TABLE 1 Case mix in the study period.

Cases	Suspected non-HIT, *n* (%)	Confirmed HIT, *n* (%)	Total cardiac operations, *n* (%)
Patients	679 (100)	29 (100)	13,178 (100)
Isolated coronary (OP)	34 (5.0)	3 (10.3)	2207 (16.7)
Isolated coronary (CPB)	11 (1.6)	0	297 (2.3)
Valvular surgery	362 (53.3)	15 (51.7)	5553 (42.1)
Combined coronary and valvular	165 (24.3)	2 (6.9)	2670 (20.3)
Aortic surgery	98 (14.4)	8 (27.6)	1954 (14.8)
Other major cardiac surgery	9 (1.3)	1 (3.4)	496 (3.8)
Total on-CPB major surgery	*646 (95.0)*	*26 (89.7)*	*10,971 (83.3)*

Study period: from February 2013 to August 2023.

Suspected non-HIT vs confirmed HIT case mix, Fisher's exact test, $P = .04$.

Confirmed HIT vs total non-HIT case mix, $P = .127$.

CPB, cardiopulmonary bypass; HIT, heparin-induced thrombocytopenia; OP, off-pump.

TABLE 2 Patients' demographics.

Demographics	HIT, *n* (%)	HIPA negative, *n* (%)	*P*
Patients, *n*	29	30	
Age, y, mean ± SD	65.83 ± 14.7	74.37 ± 9.73	.01[a]
Female	13 (44.8)	10 (33.3)	.365[b]
Hypertension	20 (69.0)	22 (73.3)	.71[b]
Diabetes mellitus	7 (24.1)	7 (23.3)	.94[b]
Dyslipidemia	12 (41.4)	14 (46.7)	.68[b]
Smokers	10 (34.5)	15 (50.0)	.228[b]
Preoperative creatinine, mg/dL, median (IQR)	0.85 (0.60)	1.31 (0.78)	.006[c]
BMI ≥ 25-30 kg/m^2	9 (31.0)	10 (33.3)	.85[d]
BMI ≥ 30 kg/m^2	5 (17.2)	5 (16.7)	1[d]
CPB	26 (89.7)	28 (93.3)	.67[d]

BMI, body mass index; CPB, cardiopulmonary bypass; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia.

[a]Levine's test for the equality of variances.

[b]Chi-squared test.

[c]Mann–Whitney U-test.

[d]Fischer's exact test.

TABLE 3 Thrombocytopenia characteristics and 4T score.

Characteristics	HIT	HIPA negative	Total	*P*
Preoperative PLT, $n \times 10^9$/L (mean ± SD)	237.1 ± 82.9	154.0 ± 58.8	194.9 ± 82.5	<.001[a]
PLT peak, $n \times 10^9$/L (mean ± SD)	192.2 ± 83.3	130.7 ± 61.7	160.9 ± 78.8	.002[a]
PLT nadir, $n \times 10^9$/L (mean ± SD)	59.1 ± 48.2	53.1 ± 28.3	56.0 ± 39.1	.563[a]
PLT change, % (mean ± SD)	65.9 ± 20.9	54.7 ± 22.3	60.2 ± 22.2	.05[a]
TP onset time, POD, median (IQR)	6 (3)	1.5 (7)	5 (6)	.175[c]
Pattern A, *n* (%)	24 (82.8)	19 (63.3)	43 (72.9)	.09[b]
Pattern B, *n* (%)	5 (17.2)	11 (36.7)	16 (27.1)	
4T score, median (IQR)	5 (1)	3 (2)	4 (2)	<.001[c]

HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; PLT, platelet count; POD, postoperative day; TP, thrombocytopenia.
[a]Levine's test for the equality of variances.
[b]Chi-squared test.
[c]Mann–Whitney U-test.

3.2 | Clinical suspicion

HIT was clinically suspected in 708 patients for whom CLIA tests were ordered. The 4T score in HIT and HIPA-negative groups is outlined in Table 3 and Figure 1. AUC for 4T score was good: 0.817 (95% CI, 0.71-0.92); $P < .001$. A cutoff of ≥4 had 99.9% NPV and 0.47% positive predictive value for HIT.

3.3 | Laboratory findings

The CLIA test was performed in all the 708 patients for whom HIT was suspected (5.37% of the whole cohort). A positive CLIA test result (≥1 U/mL cutoff, according to the manufacturer) was reported in 59 patients (0.45%). In all these cases, a functional HIPA test was performed and was positive in 29 patients (0.22%), in which diagnosis of HIT was confirmed. CLIA results were 8.9 times higher in HIT than in HIPA-negative patients ($P < .001$). The distribution of HIPA-positive patients among the CLIA classes of positivity is illustrated in Figure 2. The AUC was good (0.899; 95% CI, 0.82-0.977; $P < .001$), and the calculated cutoff of ≥2.08 still had 100% sensitivity and 97.8% specificity to detect HIPA-positive cases with 100% NPV. The incidence of suspected HIT, confirmed HIT, and HITT in patients who underwent on-pump and off-pump surgery is depicted in Table 4. Thrombocytopenia characteristics, preoperative PLT count, PLT count peak, PLT nadir, and PLT percent change in HIT and HIPA-negative groups are detailed in Table 3.

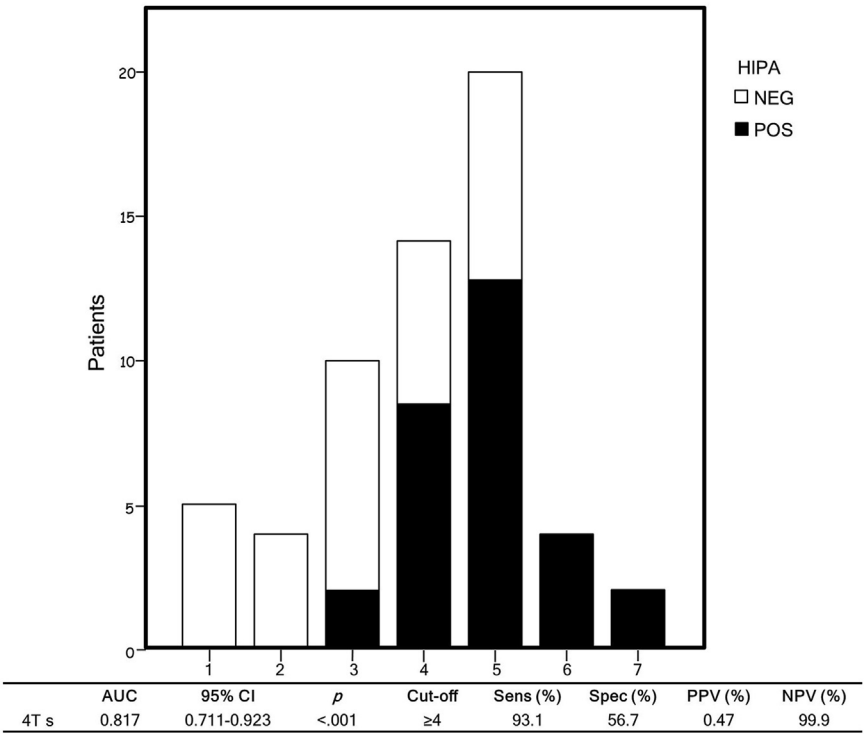
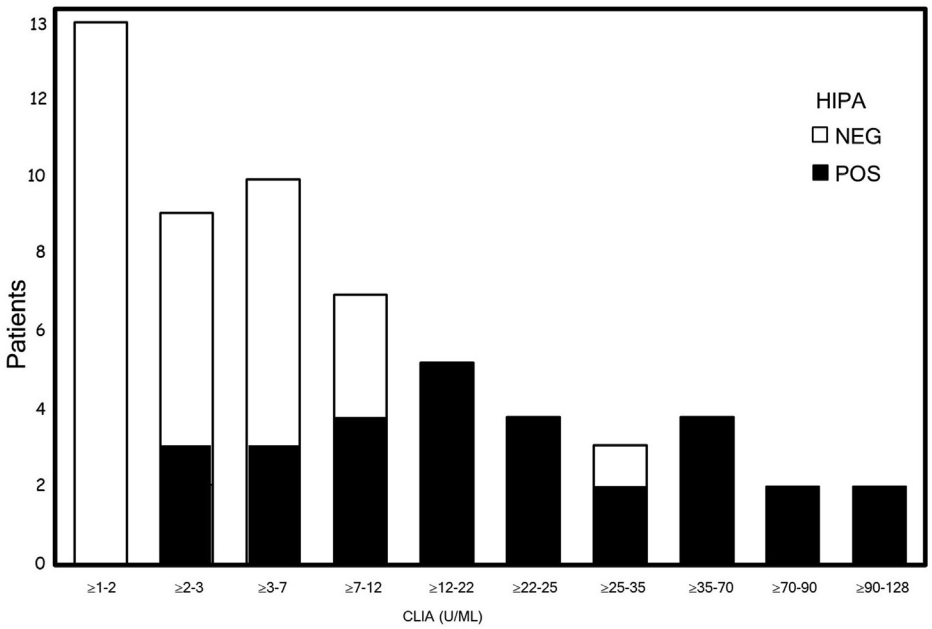


FIGURE 1 4T score in immunoglobulin G-specific chemiluminescence immunoassay-positive patients. Receiver operating characteristic curve analysis. AUC, area under the curve; HIPA, heparin-induced platelet activation assay; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.



CLIA positivity, U/ml, (IQR)		HIPA positive 19.93 (30)		HIPA negative 2.24 (2)		*p* [a] *<.001*		
CLIA, U/ml	AUC	95% CI	p	Cut-off	Sens (%)	Spec (%)	PPV(%)	NPV (%)
	0.899	0.821-0.977	<.001	2.08	100	97.8	9,07	100

FIGURE 2 Heparin-induced platelet activation assay (HIPA) positive tests in immunoglobulin G-specific chemiluminescence immunoassay (CLIA) classes of positivity and receiver operating characteristic curve analysis. AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity. [a]Mann–Whitney U-test.

3.4 | Clinical outcome

Outcome measures of HIT- and HIPA-negative groups are shown in Table 5 (and in the Supplementary Table). Two patients died at 30 days in the HIT group (6.9%); both deaths occurred in patients who had associated thrombotic complications. Three patients also died in the HIPA-negative group (10%), and 41 (6.3%) died in the CLIA-negative cohort (Supplementary Table). Thus, HIT mortality was similar to that of the suspected non-HIT patients (44 patients; 6.5%; *P* = .929). The comprehensive 30-day mortality of the whole cohort of patients undergoing cardiac surgery in the study period was 3.3% (429 patients). Cumulative mortality of the 708 patients suspected of HIT was 6.5% (46 patients), which was 2.09 times higher than that of the 12,470 patients in which HIT was not suspected (3.1%; 383 deaths; *P* < .001). Mortality of the much smaller HIT sample (6.9%) was again 2.12 times higher than that of non-HIT patients (3.2%; 427 deaths; *P* = .268), although this difference was not statistically significant.

As depicted in Table 5, HITT occurred in 6 patients (20.7% of HIT patients; 0.04% of the whole cohort). Three cases of arterial thrombosis and 4 cases of venous thrombosis were recorded. Similarly, thromboembolic complications occurred in 20% of HIPA-negative cases (*P* = .948). The clinical course of the 6 HITT cases is detailed in the Supplementary Material.

AKI of any grade occurred in 13 patients (44.8%) in the HIPA-negative group and in 16 patients (53.3%) in the HIT group (*P* = .514). CRRT was needed in 13.8% of HIT patients and in 36.7% of HIPA-negative group (*P* = .044). However, HIPA-negative patients had higher preoperative creatinine levels than HIT patients (1.31 mg/dL vs 0.85 mg/dL; *P* = .006) but similar postoperative maximum creatinine peak (1.67 mg/dL vs 1.24 mg/dL; *P* = .11).

Inotropic support was needed more often in HIPA-negative group (56.7% vs 13.8%; *P* = .001); the need for an IABP was also higher but not statistically significant in this group (20.0% vs 10.3%; *P* = .47).

Sepsis was recorded in 33.3% of HIPA-negative group and in 17.2% of HIT patients (*P* = .156).

TABLE 4 Heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis incidence over major cardiac surgery.

Groups	On-pump, *n* (%)	Off-pump, *n* (%)	*Total*, *n* (%)
Patients	10,971	2207	13,178
Suspected HIT	671 (6.12)[a]	37 (1.68)[a]	708 (5.37)
Positive CLIA test	54 (0.49)	5 (0.23)	59 (0.45)
Positive HIPA test (HIT)	26 (0.24)	3 (0.14)	29 (0.22)
HITT	5 (0.04)	1 (0.04)	6 (0.04)

CLIA, immunoglobulin G-specific chemiluminescent immunoassay; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; HITT, HIT with thrombosis.
[a]Off-pump vs on-pump (*P* < .0001), Fisher's exact test.

TABLE 5 Outcomes in immunoglobulin G-specific chemiluminescent immunoassay-positive patients.

Outcome	HIT, *n* (%)	HIPA negative, *n* (%)	Total, *n* (%)	*P*
Patients, *n*	29	30	59	
30-d mortality	2 (6.9)	3 (10.0)	5 (8.5)	1[c]
Thromboembolic events	6[a] (20.7)	6 (20.0)	12 (20.3)	.948[c]
Arterial thrombosis	3 (10.3)	3 (10.0)	6 (10.2)	1[c]
Venous thrombosis	4 (13.8)	3 (10.0)	7 (11.9)	.706[c]
AKI	13 (44.8)	16 (53.3)	29 (49.2)	.514[b]
CRRT	4 (13.8)	11 (36.7)	15 (25.4)	.044[b]
Postoperative creatinine peak, mg/dL, median (IQR)	1.24 (1.57)	1.67 (1.65)	1.41 (1.63)	.11[d]
Sepsis	5 (17.2)	10 (33.3)	15 (25.4)	.156[b]
Need for inotropic support	4 (13.8)	17 (56.7)	21 (35.6)	.001[b]
IABP	3 (10.3)	6 (20.0)	9 (15.3)	.47[c]
ECLS	1 (3.4)	1 (3.3)	2 (3.4)	1[c]
Hospital LOS, d, median (IQR)	14 (11)	16.5 (19)	15 (15)	.716[d]

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ECLS, extracorporeal cardiac life support; IABP, intra-aortic balloon pump; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; LOS, length of stay.
[a]One patient had both arterial and venous thrombosis.
[b]Chi-squared test.
[c]Fischer's exact test.
[d]Mann–Whitney U-test.

Median hospital LOS was also higher in HIPA-negative group (16.5 days; IQR, 19 days) than in HIT patients (14 days; IQR, 11 days), although this difference was not statistically significant (P = .716).

3.5 | Pharmacologic management

Pharmacologic management of HIT patients is summarized in Table 6. Heparin was suspended in all the patients and replaced with an alternative anticoagulant, which was subcutaneous fondaparinux in most cases (18; 62.0% of patients). Bivalirudin was used in 3 cases (10.3%) to manage anticoagulation during extracorporeal life support and for CPB. Vitamin K antagonist (VKA) use was influenced by the onset time of HIT since this diagnosis was often made several days after surgery (median, 6; IQR, 3) when VKA had already been started. In 3 patients (12.5%), VKA was stopped, and it was replaced by an alternative anticoagulant at the time of HIT diagnosis. It was started again only after the PLT count had recovered. In 2 patients, VKA was started early but stopped for other reasons before the diagnosis of HIT was made. In 3 other patients (12.5%), VKA was started after HIT was diagnosed, imbricating it with fondaparinux, but only when PLT count had begun to recover after the PLT nadir (52×10^9/L, 67×10^9/L, and 79×10^9/L, respectively). In 16 (55.1%) other patients in which VKA was started early on the second POD after surgery, it was not suspended when the diagnosis of HIT was made, having been started from more than 5 days, and the international normalized ratio was steadily in the therapeutic range at that time. No new thromboembolic complications were registered in any of these 16 patients.

TABLE 6 Heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis pharmacologic management.

Drug	Stopped, *n* (%)	Started/continued, *n* (%)
Heparin	29 (100)	0
Fondaparinux	0	18 (62.0)
Bivalirudin[a]	0	3 (10.3)
Vitamin K antagonists	5 (17.2)[b]	19 (65.5)[c]
DOAC	0	1 (3.4)
Danaparoid	0	1 (3.4)

DOAC, direct oral anticoagulants.
[a]For extracorporeal cardiac life support management in 2 heparin-induced thrombocytopenia with thrombosis patients.
[b]Stopped and restarted in 3 patients according to current guidelines. Stopped in 2 patients before heparin-induced thrombocytopenia diagnosis.
[c]Started before complete platelet count recovery in 3 patients (2 heparin-induced thrombocytopenia with thrombosis). Started early in the immediate postoperative period and continued in 16 patients because the international normalized ratio was in the therapeutic range at the time of diagnosis.

4 | DISCUSSION

The cardiac surgery setting is universally considered at high risk of HIT [5] since high dose UFH is required for both off-pump and on-CPB procedures (150-200 and 300-400 IU/kg, respectively). Moreover, both UFH and low-molecular-weight heparin are widely used before and after surgery both for thromboembolic prophylaxis and to achieve stable anticoagulation in some conditions that are common in the perioperative period (eg, percutaneous interventions, IABP, extracorporeal cardiac life support, and CRRT). Therefore, in this setting, both the trigger for HIT antibody production and the continuous heparin exposure are typically present, which could trigger the clinical picture of HIT.

4.1 | Incidence

Since HIT is a very rare condition, our knowledge about it comes mostly from retrospective studies performed over prolonged periods of time, case reports, or case series. HIT occurrence after cardiac surgery has been variably reported in 0.2% to 3% of patients [5,6]. We present a large, retrospective study conducted over a 10-year and 6-month period in a single, high-volume cardiac surgery center. In our series, PF4/H-ab tests were frequently ordered (5.37%). Nonetheless, as illustrated in Table 4, isolated HIT was confirmed in 29 patients (0.22%) over a total of 13,178 cardiac operations. Thrombosis occurred in only 6 patients (20.7%) with HIT (0.04% of the entire cohort), which was lower than that reported in other studies (38%-81%) [15].

Notably, 2207 OPCABG patients were included in our series. To the best of our knowledge, this is the first report on HIT that includes such a large number of OPCABG procedures. Although these operations are performed without CPB, they similarly require high heparin dose. Suspicion of HIT arose more often in the CPB cohort than in OPCABG (6.12% and 1.68%, respectively; $P < .001$). Although CLIA tested positive for PF4/H-ab (≥1 U/mL) in 0.49% of CPB procedures and in 0.23% of off-pump procedures ($P = .089$), the incidence of confirmed HIT and HITT between the 2 groups were quite similar (Table 4). Therefore, the use of CPB, while being a trigger for antibody formation, did not appear to affect the actual incidence of HIT and HITT, as well as the type of surgery; notwithstanding a slightly higher rate of aortic surgery was recorded in HIT patients but less combined valvular and coronary artery bypass graft operations (Table 1).

When comparing patients with HIT- and HIPA-negative patients, the latter were older (74.37 years vs 65.83 years; $P = .01$), but no other significant differences were detectable between these groups preoperatively, apart from serum creatinine that was 1.54 times higher in HIPA-negative group ($P = .006$).

4.2 | Diagnosis

It is recognized that the diagnosis could be challenging in the cardiac surgery setting, where thrombocytopenia is quite common. This can be due to heparin, but in absence of an immunologic mechanism (type 1 HIT), and to other causes, such as the interaction between PLTs and the CPB circuit, surgical bleeding, transfusions, drugs, or infections [16]. Thromboembolic complications due to other causes are also common after cardiac surgery, and therapeutic anticoagulation with heparin is usually initiated in these cases [17]. The timing of PLT count decrease, which is one of the key points on which the 4T score is calculated, could be difficult to interpret after cardiac surgery since a high dose of heparin is administered for the procedure, but heparin could also have been used in the previous days. Also, PLT count decrease, typical of type 2 HIT, could be confounded by the transient PLT count decline usually seen in the first 72 hours after cardiac operations [5]. In our study, a typical onset profile, usually biphasic (pattern A), was the most frequent presentation pattern of PLT count decrease in HIT patients (82.8%), as it was reported by others [18]. Nonetheless, in 17.2% of cases, a rapid onset profile (pattern B) could also be recognized. This could be due to already circulating PF4/H-ab when heparin was given for surgery. Pattern A is so frequent after cardiac surgery that an alternative score based on this presentation has been suggested in this setting [12]. Conversely, pattern B has been reported to occur almost exclusively in patients previously exposed to heparin [19]. In our cohort, 13 (44.8%) HIT patients had been exposed to heparin before the operation. Of these, 4 (30.8%) had a rapid pattern profile, while only 1 (6.2%) had such a profile without a previous heparin exposure. In our series, an early onset profile was rarely associated with HIT unless the patient had been previously treated with heparin, as reported by others [18].

Although the mean PLT count nadir after cardiac surgery was like that reported for HIT in other settings [19], it was not uncommon to see a PLT nadir of $<20 \times 10^9$/L in our series (5 patients; 17.2%).

The lower preoperative PLT count and PLT peak in the HIPA-negative group, as compared with the HIT group, could be explained by the presence of other causes of thrombocytopenia (eg, sepsis) that may have preceded surgery in HIPA-negative patients.

The onset time of thrombocytopenia and its presentation pattern were the most differentiating characteristics between the HIPA-negative and HIT patients, taking into account that a rapid onset HIT could be suggested only if preceded by a previous exposure to heparin.

Moreover, our analysis confirmed that the 4T score had a high 99.9% NPV for excluding HIT.

In a cardiac surgery setting, a specific immunologic test is even more pivotal than in other settings to avoid unnecessary functional tests and promote an early diagnosis. Although in our series, the CLIA test reported a broad spectrum of positive results, a cutoff of ≥1 U/mL was considered a marker of positivity, and HIPA test was performed only in these cases. A positive CLIA test was recorded in 59 patients (0.45%), while HIPA tested positive in 29 (0.22%).

CLIA test positivity was 8.9 times stronger in HIPA-positive than in HIPA-negative patients ($P < .0001$). Although the manufacturer recommends a cutoff of ≥1 U/mL, the ROC analysis on our data indicated that a cutoff of ≥2.08 U/mL still had a 100% NPV to exclude HIT. However, this is in contrast with other reports that indicate a risk of false negative results even with the 1 U/mL cutoff [9]. Therefore, guidelines recommend preferring lower cutoffs for diagnosis to avoid the risk of false negatives and missing potentially life-threatening diagnoses [20]. Conversely, a positive CLIA result of ≥12 U/mL was highly predictive of a positive HIPA result (Figure 2).

4.3 | Outcomes

Mortality of the 29 HIT patients was higher (6.9%) than the overall mortality of the cardiac surgery population from which they were extracted (3.3%). However, cumulative mortality of the 679 thrombocytopenic suspected but non-HIT patients (6.5%) was like that of HIT patients ($P = .929$). As has already been suggested by others,

thrombocytopenia may be interpreted as a negative prognostic sign since it could indicate the presence of a life-threatening underlying pathology irrespective of the presence of HIT antibodies [6]. Notably, 33.3% of the patients in HIPA-negative group had sepsis during their postoperative course.

The cause of death in the HIT group was related to thromboembolic complications. Thromboembolic complications were reported only in 6 HIT patients. Therefore, the low incidence of thromboembolic complications in this group (20.7%) could also explain the low HIT mortality in this study (6.9%) with respect to other reports [6]. The incidence of HIT (0.22%) and HITT (0.04%) in our cohort was lower than that found by other authors in this setting [5]. Moreover, of the 6 recorded HITT patients, only 3 had a new onset thrombosis in the postoperative period; the other 3 already had thrombosis on presentation to the hospital, and in 2 of them, no previous heparin exposure was recorded. Therefore, only 3 HITT (1 OPCABG and 2 CPB) could be acknowledged as unambiguous cases of postoperative thrombosis occurring after heparin administration in patients with acute ongoing HIT (Supplementary File).

Postoperative AKI occurred with similar rates in HIPA-negative group and HIT patients, while CRRT was needed more in the former (36.7% vs 13.8%; P = .044). However, the HIPA-negative group had higher baseline creatinine level (Table 5).

HIPA-negative patients also had a significantly greater need for inotropic support (56.7% vs 13.8%; P = .001).

The hospital LOS did not show significant differences between groups, although it appeared longer in HIPA-negative patients (16.5 days vs 14 days; P = .716).

All these findings could be interpreted as further evidence that patients with significant thrombocytopenia after cardiac surgery are at elevated risk, regardless of the cause.

4.4 | HIT and HITT management

Current guidelines do not specifically address the treatment of HIT after cardiac surgery. However, they generally recommend replacing heparin with an alternative anticoagulant when HIT is suspected or confirmed, balancing the risk of bleeding, which is high after cardiac surgery, against that of HIT complications [5,20,21]. Conversely, they recommend against initiation of VKA before the PLT count recovers (usually a PLT count of $\geq 150 \times 10^9$/L) and to stop and reverse VKA when it is still in use [5,20]. In the totality of our patients with a positive HIPA test, heparin was suspended and replaced by an alternative anticoagulant in accordance with current guidelines [5,20,21]. Fondaparinux was the most extensively used (62%) alternative anticoagulant in HIT patients. More recently, after its introduction on the Italian market, danaparoid has also been used in 1 patient. The PLT count recovered in every case in which heparin was replaced by fondaparinux or danaparoid, and no new thromboembolic event occurred. Although the evidence in favor of fondaparinux for anticoagulation in HIT is of low quality, and a few case reports even suggested the occurrence of a fondaparinux-induced HIT [5], this drug has shown to be safe and effective in our practice. Also, in 16 patients where warfarin was initiated before the diagnosis of HIT, it was neither suspended nor reversed with vitamin K. In these cases, diagnosis was suspected or made at a time point after surgery when the international normalized ratio was already in the therapeutic range. Although warfarin was not suspended in these patients, no thromboembolic complications occurred. This could be ascribed to the fact that oral anticoagulation was reached before antibody formation, as VKA was started early after surgery. This could have protected patients from the effect of PF4/H-abs. The same reason was suggested by others to explain the different frequencies of HIT between countries. The early initiation of warfarin in Scandinavia and the Netherlands in the early 1990s, limiting the time of heparin treatment to 4 to 5 days, was considered the most probable reason why HIT was less frequently reported in these countries than in Germany and France [22]. This could also be an explanation for the low incidence of HIT and HITT in our cohort. Moreover, since warfarin was usually administered for more than 5 days before onset of HIT, thrombin inhibition could have already balanced the earlier protein C inhibition at that time (visual summary) [23]. In 3 other cases, warfarin was started after the diagnosis was made and after fondaparinux initiation, but before that, the PLT count had recovered to the acknowledged safety value of 150×10^9/L indicated by guidelines [5,20]. Of note, in 2 of these patients, although thrombotic complications had already occurred, no new thrombosis took place, even if the PLT count was under 100×10^9/L at the time of warfarin initiation. According to guidelines, warfarin should not be used in the acute phase of HIT. However, in the cardiac surgery setting, where warfarin can be started well before (>5 days) HIT occurs, a careful clinical evaluation with the help of an expert in thrombosis and hemostasis is advisable to establish the anticoagulation strategy on a case-by-case basis.

4.5 | Limitations of the study

The main limitation of the present investigation is its retrospective design. We performed many tests, even with a 4T score below 4. Although it may be unlikely that some HIT diagnoses have been missed, it cannot be ruled out.

In addition, what has been described about warfarin could be the result of the specific anticoagulation protocol in use in our department, which may not be valid for others.

No inference about BMI can be made due to the high rate of missing values in this variable. However, analysis with complete cases did not show any difference in BMI between groups.

Moreover, the study includes a small number of HIT cases with a limited number of thromboembolic events. Therefore, the establishment of an international HIT registry or a large multicenter study performed over a prolonged period of enrolment would be needed to obtain a significant sample of patients and events.

5 | CONCLUSIONS

In conclusion, the incidence of HIT and HITT after cardiac surgery was rather low in our institution, independent of the type of surgery and the use of CPB.

Diagnosis was challenging in this cohort, but it was improved by combining the 4T score with the highly specific CLIA test. A typical PLT count pattern, together with the onset time of thrombocytopenia ≥ POD 5, could help suggest HIT in most cases. Conversely, PLT drop with a rapid pattern B or an earlier onset time was seldom associated with HIT unless previous heparin had been administered.

Pharmacologic management of HIT and HITT was based on heparin suspension and alternative anticoagulation with fondaparinux, direct thrombin inhibitors, and, more recently, danaparoid. Warfarin was started early in most cases, and although it was often continued even after the diagnosis of HIT was made, no new thromboembolic events occurred in these patients.

Future large prospective studies or international registries are needed to confirm these findings and to improve the current knowledge and the quality of scientific evidence on this rare but fearful condition.

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RELATIONSHIP DISCLOSURE

The authors have no competing interests to disclose.

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SUPPLEMENTARY MATERIAL

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