CLINICAL INVESTIGATIONS

Characterization of hospitalized cardiovascular patients with suspected heparin-induced thrombocytopenia

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Background: Little is known about heparin-induced thrombocytopenia (HIT), a pro-thrombotic, potentially life-threatening immune-mediated reaction to heparin exposure, in conservative and interventional cardiovascular medicine.

Hypothesis: The 4T score, validated for prediction of HIT in surgical patients before, is also suitable for assessing HIT probability in cardiovascular patients with unclear thrombocytopenia.

Methods: A total of 403 consecutive patients from our Department of Cardiology, Angiology and Pneumology in whom a HIT screening test was performed between 2009 and 2016 were identified. All 72 patients with a positive screening test were subjected to a functional confirmation test (heparin-induced platelet activation test, HIPA), resulting in 23 patients with serologically confirmed HIT (positive screening test, positive HIPA) and 49 patients with nonconfirmed HIT (positive screening test, negative HIPA).

Results: The 4Tscore had a sensitivity of 82.6% and a specificity of 28.6% in our patients, suggesting that it might not sufficiently predict the clinical probability of HIT in cardiovascular patients. In both confirmed and nonconfirmed HIT, intrahospital mortality was high without a significant difference (30% in confirmed HIT vs 43% in nonconfirmed HIT). Bacteremia was more often found in patients with nonconfirmed HIT, suggesting infection as a frequent differential diagnosis of thrombocytopenia in these patients (49% vs 17%, $P = 0.0185$).

Conclusion: HIT screening should be initiated in cardiovascular patients with unclear thrombocytopenia despite a low 4Tscore in order to distinguish patients requiring alternative anticoagulants from those with other causes such as infections. Further research is needed to specify the risk profile for HIT in cardiovascular patients.

KEYWORDS

heart failure, heparin, HIT, thrombocytopenia

1 | INTRODUCTION

Heparin-induced thrombocytopenia (HIT) is a pro-thrombotic, potentially life-threatening immune-mediated reaction to heparin exposure.¹ Platelet-activating antibodies binding to the complex of heparin and platelet factor 4 (PF4) are formed.² The typical clinical presentation is marked by a drop of the platelet count 5 to 14 days after the first heparin dose, and the occurrence of arterial or venous thrombosis. Due to the frequent use of heparin, HIT—even if relatively rare—can be considered one of the most important adverse drug reactions overall.³

Although alternatives for the anticoagulation in atrial fibrillation and thromboembolies have emerged with the introduction of the direct oral anticoagulants (DOACs), heparin remains the anticoagulation of choice in the growing field of interventional cardiovascular medicine, and is still used in patients with mechanical valves, ventricular assist devices (VAD), or when DOAC treatment is not possible, for example, due to impaired renal function.

While on the one hand missing the diagnosis can be fatal, overdiagnosis of HIT on the other hand presents a significant problem and is mainly related to the diagnosis of HIT only based on the presence of antibodies in disregard of further evaluation by a

functional test. While the frequently used immunoassays can detect the presence of antibodies against the complex of heparin and platelet-activating factor 4 as a screening test, the serological diagnosis of HIT is only confirmed when these antibodies show platelet-activating properties.⁴

Not in all patients with a positive screening test, the presence of platelet-activating antibodies can be confirmed. These patients have various reasons for thrombocytopenia and are not considered to have an elevated risk of thrombosis.^{4,5} Nevertheless, we found this group worth of further characterization in addition to the group of patients with confirmed HIT.

While the clinical course of surgical patients is well described,^{4,6,7} little is known about HIT in conservative and interventional cardiology. Therefore, we characterized a cohort of cardiovascular patients with suspected HIT and compared the groups with serologically confirmed and nonconfirmed HIT regarding demographics, clinical parameters, outcome, and the value of the 4Tscore in those patients.

2 | METHODS

2.1 | Study design

We identified 403 consecutive patients from our Department of Cardiology, Angiology and Pneumology in whom serological tests for HIT were performed between 2009 and 2016. Seventy-two patients with a positive screening test (particle gel immunoassay [PaGIA] test in the majority of patients) were included and further characterized (Figure 1). The 4Tscore was calculated retrospectively from the recorded clinical and laboratory data. Approval of the local ethics committee was obtained.

2.2 | Laboratory assays

The particle gel immunoassay (PaGIA) test (Biorad, Oberschleissheim, Germany) was performed in patients from 2010 on with suspected HIT (negative predictive value 98%-99% and positive predictive value 10%-40%). Before 2010, an Enzyme-linked Immunosorbent Assay (ELISA) test (Asserachrom (R) HPIA, Stago Deutschland GmbH, Düsseldorf) was performed as a screening test. In patients with a positive screening test, a functional test (heparin-induced platelet activation test, HIPA) was initiated for further evaluation.

2.3 | Statistical analysis

Comparisons between the groups of serologically confirmed HIT (=positive screening test, positive HIPA) and nonconfirmed HIT (=positive screening test, negative HIPA) were made with the independent *t* test and the χ^2 test (Fisher exact test for samples <5). A *P*-value <0.05 was considered statistically significant. Statistical analysis was performed with SPSS (IBM SPSS Statistics for Windows, Version 24.0., IBM CorpArmonk, NY, USA). Data are given as mean $\pm$ SD.

3 | RESULTS

The leading cause of hospital admission in this cohort was decompensated heart failure (53%). At the time of serological HIT diagnostics, 85% of all patients were treated on the intensive care unit, cardiac care unit or heart failure unit. Three quarters of all patients had a cardiac ejection fraction (EF) of less than 45%, and EF was below 30% in 61% of all patients (Table 1).

The most common indication for anticoagulation was atrial fibrillation (62.5%), followed by acute coronary syndrome (ACS) (19.4%), venous thromboembolism (11.1%), prosthetic valve (8.4%), cardiac device (6.9%), and/or arterial/left ventricular (LV) thrombus (5.6%).

FIGURE 1 Outline of the study. Out of 403 patients in whom HIT diagnostics had been performed, those with a positive screening test were selected. HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia

TABLE 1 Comparison of demographic and cardiac characteristics between patients with confirmed and nonconfirmed HIT. If not otherwise specified, table shows absolute numbers of patients and percentages in brackets

	HIPA+ (n = 23)	HIPA- (n = 49)	P-value
Age	64 ± 15 years.	67 ± 14 years.	0.357
Male	16 (69.6%)	36 (73.5%)	0.73
EF < 45%	17 (73.9%)	37 (75.5%)	0.884
EF < 30%	14 (60.9%)	30 (61.2%)	0.978
Decompensated heart failure	14 (60.9%)	24 (49.0%)	0.346
Atrial fibrillation	14 (60.9%)	31 (63.3%)	0.845
Aortic stenosis III	5 (21.7%)	9 (18.4%)	0.74
Catheter-based intervention	17 (73.9%)	32 (65.3%)	0.465

Abbreviations: EF, ejection fraction; HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia.

Between patients with serologically confirmed HIT (n = 23) and patients with nonconfirmed HIT (n = 49), there was no significant difference regarding age, sex, prevalence of congestive heart failure, atrial fibrillation, and severe aortic stenosis, or previous catheter-based interventions including coronary angiographies, right-heart catheter, valvuloplasty, transcatheter aortic valve replacement (TAVR), and percutaneous transluminal angioplasty (Table 1). There were seven patients treated with a TAVR. In two of these patients, HIT was confirmed ($P = 0.6$).

The platelet count ($104/\text{nl} \pm 111$ with HIT vs $103/\text{nl} \pm 77$ with r/o HIT at the time of the PaGIA test) as well as the 4 T-Score, evaluating thrombocyte count, timing of thrombocytopenia, thrombotic events, and possible other reasons for thrombocytopenia, did not significantly differ either (4.7 ± 1.5 for confirmed vs 4 ± 1.5 for ruled-out HIT, $P = 0.074$). The 4TScore was ≤ 3 in 17.4% of patients in whom HIT was confirmed serologically. In our patients, we found a sensitivity of the 4TScore of 82.6%, and a specificity of 28.6% (Table 2).

All patients in whom HIT was confirmed had a previous exposure to unfractionated heparin (UFH) (100%), while there were two patients having received only low molecular heparin in the HIT ruled-out group (exposure to UHF 96%). The platelet nadir was $76/\text{nl} \pm 56$ for the patients with confirmed HIT, and $80/\text{nl} \pm 70$ with ruled-out HIT ($P = 0.72$).

56.5% of patients with confirmed HIT had ≥ 1 thromboembolic event before or after the time of diagnosis (36.7% of patients with nonconfirmed HIT, $P = 0.11$). In the patients with serologically confirmed HIT, thrombosis was more often evident already at the time of the serological HIT test than in the other group (Table 3). Arterial thrombosis in the HIT patients included ischemia of inner organs such as renal or splenic infarction as well as apoplexy and extended arterial thrombosis of the lower extremity, while in the group in which HIT was serologically ruled out, there was apoplexy, myocardial infarction and thrombosis of the *Arteria radialis*, all possibly related to other reasons, including interventions.

TABLE 2 Clinical probability of HIT based on the 4TScore

	4TScore ≤ 3	4TScore > 3	
HIPA-	n = 14	n = 35	Specificity: 28.6%
HIPA+	n = 4	n = 19	Sensitivity: 82.6%
	Negative predictive value: 77.8%	Positive predictive value: 35.2%	

Abbreviations: HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia.

Patients with nonconfirmed HIT were significantly more often found to have bacteremia (49% vs 17%, $P = 0.0185$; Figure 2). Furthermore, there was a trend toward previous open-heart surgery in patients with confirmed HIT (13%, all valve surgery) compared to those without HIT (6.1%, $P = 0.3$).

There was no significant difference in neoplasms in patients with confirmed HIT (4.3% vs 10.2% in patients with nonconfirmed HIT, $P = 0.657$).

With the clinical suspicion of HIT, heparin was stopped immediately and substituted with an alternative anticoagulant (83.3%) except if clinical suspicion was low or if there was a contraindication such as severe bleeding. 83.3% were treated with argatroban, 8.3% with fondaparinux, and 3.3% with danaparoid. Argatroban resulted in therapeutic elevation of the activated partial thromboplastin time (PTT) in 68.2% of treatment days per patient. In 22% of patients, bleeding events were reported under argatroban; none were registered for fondaparinux or danaparoid.

Intrahospital mortality was 30% for the patients with confirmed HIT, and 43% for patients with ruled-out HIT ($P = 0.313$).

Of all 403 patients in whom a HIT screening test was initiated in the first place, serological HIT was confirmed in 5.7%.

4 | DISCUSSION

In our study on HIT in cardiovascular medicine, the majority of patients were admitted with congestive heart failure; most of them were critically ill and had to be treated in special care units. The overall prognosis was poor, reflected by high intrahospital mortality in patients irrespective of whether HIT was confirmed or not. This is in accordance with a recent meta-analysis of patients with ACS, which showed that in-hospital acquired thrombocytopenia was associated with a higher risk of mortality as well as re-infarction, stent thrombosis and heart failure.⁸ Another recent, multicenter retrospective study found that a lower thrombocyte count, measured within 1 month

TABLE 3 Prevalence of thromboembolic events (≥ 1 per patient) in the patients with serologically confirmed HIT and those with nonconfirmed HIT. UE thrombosis, mostly associated with central line

	HIPA+		HIPA–	
	Total	Prior to HIT test	Total	Prior to HIT test
Arterial	5 (38.5%)	3	8 (38.1%)	3
Venous—of which UE	8 (61.5%) 5 (62.5%)	7	13 (61.9%) 9 (69.2%)	8
Total	13	10 (76.9%)	21	11 (52.4%)

Abbreviations: HIPA, heparin-induced platelet activation; HIT, heparin-induced thrombocytopenia; UE, upper extremity.

after the diagnosis of reduced ejection heart failure, was a marker for a higher 1-year mortality in these patients.⁹ Mortality in our study was higher than expected from other HIT studies,¹⁰ most likely reflecting the high burden of morbidity in our heart failure patient collective.

Comparing patients with serologically confirmed HIT to the ones with HIT rule-out, we could not find any significant difference regarding core functional cardiac parameters, above all EF. However, we did notice a significantly higher presence of bacteremia in patients with nonconfirmed HIT compared to those with confirmed HIT. This stresses the importance of considering alternative causes of thrombocytopenia in patients with suspected HIT. Among others, thrombocytopenia has long been known as a marker for a severe infection; the thrombocyte count is one of the six criteria of the sepsis-related organ failure assessment score.^{11,12} Furthermore, thrombocytopenia has been found to increase the risk of death in intensive care unit (ICU) patients.¹³ Several drugs, among them frequently used antibiotics, are also suspected to cause thrombocytopenia.¹⁴ In our patient collective, almost all patients had been administered at least one medication for which thrombocytopenia is listed as a potential side effect in the drug information; medication included furosemide, tazobactam/piperacilline, atorvastatin, and pantoprazole. However, in a case-matched study of 238 patients with ICU-acquired thrombocytopenia, no association of thrombocytopenia with drugs could be confirmed except for quinolones.¹⁵

It has to be noted that in gram-negative bacteremia, the PF4/lipopolysaccharide complex can induce the formation of cross-reacting antibodies against PF4/heparin, blurring the boundaries between HIT and sepsis.^{16,17} However, in our study, bacteremia was significantly less frequent in patients with positive ELISA or HIPA test.

Greinacher *et al*⁵ found HIT to be confirmed in only 5.6% of patients with suspected HIT; our data met this number very closely (5.7%). The 4 T-Score, used for clinical risk assessment, was surprisingly not significantly higher in patients with HIT confirmed by a positive HIPA test in our study. A 4TScore of ≤ 3 indicates a HIT probability below 5%³ and suggests continuation of heparin without any further testing.¹⁸ This recommendation is in line with a previous study in surgical-medical ICU patients, where a low 4TScore was observed in only 1.5% of patients with confirmed HIT.¹⁹ However, our study revealed a low 4TScore in four (17.4%) of the patients with HIT later confirmed by a positive HIPA test, suggesting that HIT might be missed in cardiovascular patients with a low 4T-score. Differences in the 4TScore might be also explained by variations in the physicians' scorings, especially when evaluating the forth criteria of the score, the "other" reasons for thrombocytopenia.¹⁹ With a sensitivity of 82.6%, the 4TScore did not sufficiently predict the clinical probability of HIT in our group of cardiovascular patients, and with 28.6% it was too nonspecific for clinically differentiating HIT from other reasons of thrombocytopenia. To our knowledge, the 4TScore has never been evaluated before in cardiovascular patients and—from what we found in our study—might not display their risk well enough. In cardiac surgery where thrombocytopenia presents a common postoperative finding due to cardio-pulmonary bypass and hemodilution, further specific factors have been identified for evaluating the clinical probability of HIT, including not only the platelet count pattern, but also the duration of and time from cardio-pulmonary bypass.²⁰

While the incidence of HIT in cardiac surgery is well described and above all attributed to cardio-pulmonary bypass, literature on HIT in both conservative and interventional cardiology is sparse, although UFH remains not only the peri-operative but also the interventional gold standard. Devesa-Cordero *et al*²¹ present a first case report of lethal HIT after TAVR—a major drawback being that the diagnosis was based on the sole presence of PF4/Heparin-complex-antibodies while there was no confirmation test. Telila *et al*²² recently systematically examined the effect of HIT on the intrahospital mortality of TAVR patients in the US nationwide database and found a positive correlation. The cumulative incidence of HIT in the postinterventional period was 0.49%. This is similar to the incidence of 0.4% in a previous study of surgical-medical ICU patients²³ and by far lower than reported from conventional valve surgery where the postoperative incidence was

FIGURE 2 Frequency of positive blood cultures comparing patients with nonconfirmed and confirmed heparin-induced thrombocytopenia (HIT). Bacteremia was significantly more often found in the blood cultures of the patients with serologically nonconfirmed HIT

2.8% in a recent study.²⁰ An analysis of the US Nationwide Inpatient Sample that included not only valve patients, but all cardiac surgery patients found an HIT incidence of only 0.3%.²⁴ In our study, the number of patients after cardiac surgery was small, but they were indeed overrepresented in the HIT-positive group, all of them having received valve surgery.

The new direct oral alternative anticoagulants (DOAC) potentially facilitate the avoidance of heparin on the one hand and might present a treatment option in (suspected) HIT on the other hand. Regarding the clinical use of DOACs in HIT, there are various case reports and a couple of small studies.^{25,26} So far, fondaparinux remains the only guide-line recommended, but off-label alternative treatment option to argatroban, lepirudin, desirudin, bivalirudin, and danaparoid.²⁷

Questions also remain about the prevention and treatment of HIT in patients with mechanical valves or VAD. Little is known about the management of HIT-positive VAD patients in general, except for some experience from case reports.²⁸ In a small collective of VAD patients, thrombocyte function was impaired in all patients after implantation of the device, but also frequently prior to implantation.²⁹ This indicates that thrombocytopenia might be a common finding in end-stage heart failure; platelet abnormalities in these patients have been known for a long time, but yet have to be fully understood.³⁰

Interestingly, even when HIT is suspected but serologically not confirmed, thrombocytopenia appears to be associated with a poor prognosis in cardiovascular patients. Severe infection, that is, bacteremia, should be considered as an alternative cause of thrombocytopenia.

Taken together, HIT screening should be initiated in cardiovascular patients with unclear thrombocytopenia in order to identify patients requiring alternative anticoagulants. Using the 4TScore, HIT diagnosis would have been missed in 17.4% of our patients. Therefore, serological HIT testing should be encouraged in cardiovascular patients even when the 4TScore is low. More research on the HIT risk factors in cardiovascular patients, especially in heart failure, is needed. In an increasingly more interdisciplinary approach to patient care in cardiovascular medicine, one should also be aware of differences in HIT risk profiles between cardiac-surgical and primarily medical patients.

CONFLICT OF INTEREST

The authors declare no potential conflict of interests.

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