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# Heparin-Induced Thrombocytopenia in Iranian Cardiac Surgery Patients Using the 4Ts Clinical Scoring System and Laboratory Methods

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**ABSTRACT**

**Background:** Heparin-induced thrombocytopenia (HIT) is a serious adverse drug reaction. HIT diagnosis needs an algorithmic approach including clinical evaluation and laboratory tests (screening and confirmatory). Few studies have been conducted on HIT in Iran, and most existing research has been general and based on clinical evaluations alone. The present study was conducted to determine the prevalence of HIT among cardiac surgery patients using an algorithmic approach.

**Materials and Methods:** A cross-sectional study was carried out over a period of 10 months, at Modares Hospital (Tehran, Iran) on 92 patients who were candidates for cardiac surgery. For the clinical evaluation, the 4Ts scoring system was used; in cases with 4Ts scores ≥4, a laboratory evaluation of anti-PF4/heparin antibody (Ab) was performed by enzyme-linked immunosorbent assay (ELISA) and a HIPA test too as a functional confirmatory method. The patients with 4Ts scores ≥4 who were ELISA positive (OD ≥0.2) and HIPA positive were taken as a definite case of HIT.

**Results:** Of the 92 patients who had undergone cardiac surgery, 14 (15%) had 4Ts scores ≥4. Anti-PF4/heparin Ab was detected in eight patients using the ELISA and in six patients using the HIPA. Ultimately, definite HIT was confirmed in five of the patients.

**Conclusion:** The prevalence of HIT was 5.4% among the cardiac surgery patients assessed in the present study. To the researchers' knowledge, this is the first time that HIT has been evaluated in Iran using a comprehensive algorithmic approach including clinical history-taking and both immunological and functional laboratory tests, and the findings showed a slightly higher HIT frequency in this single-center study in comparison with the other studies carried out in other countries.

**Keywords:** Heparin; Thrombocytopenia; Diagnosis; Laboratory testing; Cardiac surgery

## INTRODUCTION

Heparin is an anticoagulant that is widely used during cardiac surgery. Heparin-induced thrombocytopenia (HIT) is a life-threatening adverse side effect of heparin that occurs in 1-3% of cardiac surgery patients[1]. There are two types of HIT: Type 1, which is a transient, non-immune and self-limiting thrombocytopenia, called heparin-associated thrombocytopenia (HAT). HAT occurs in up to 10-25% of patients during the first four days after exposure to heparin[2], and type 2, or the so-called "true HIT", which is an immune-mediated

reaction caused by IgG formation against PF4/heparin complexes. Immune complexes bind to the Fcγ receptors of platelets and monocytes, resulting in platelet activation, thrombin generation and finally a high risk for arterial and venous thrombotic complications with an increased risk of morbidity and mortality[3, 4]. The incidence of HIT varies by clinical situation, type of heparin (UFH: unfractionated heparin > LMWH: low-molecular-weight heparin), the route of administration (intravenous > subcutaneous) and gender (female > male)[5]. Due to the thrombotic risk, the immediate diagnosis of HIT is necessary for continuing or changing heparin to alternative anticoagulants like Argatroban[3].

The diagnosis of HIT is challenging in post-cardiac surgery patients because thrombocytopenia is a frequent and multifactorial finding in this group of patients. There is a high rate (25-70%) of anti-PF4/heparin Ab sero-positivity in this group of the population, and 4% to 20% of them are pathogenic, and the rate of HIT is 1-2%[6,7]. Since HIT is a clinicopathologic syndrome, its diagnosis needs a standardized clinical and laboratory evaluation. The most common clinical detection system is 4Ts scoring system, which consists of four parameters: (1) The degree of *thrombocytopenia*, (2) The *time* of platelet count reduction after exposure to heparin, (3) The occurrence of clinical events of *thrombosis* and necrosis, and (4) Excluding *other* causes of thrombocytopenia (Table 1)[8,9].

In patients who are suspected of HIT according to the 4Ts scoring system (4Ts score ≥4), laboratory evaluation is necessary to prevent over-diagnosis. There are two groups of laboratory assays for the diagnosis of HIT. First, screening immunoassays (i.e. ELISA), which detect antibodies against the PF4/heparin complex. Immunoassays characteristically have a high sensitivity for detecting weak and strong anti-PF4/heparin Ab, but only the strong Abs cause platelet activation and are pathologic. To discriminate between them, the second group of tests is needed as a confirmatory functional assay [10, 11]. Serotonin release assay (SRA) and heparin-induced platelet aggregation (HIPA) tests are two commonly-applied functional assays using washed platelets. In these tests, platelet activation occurs at low (0.1 to 0.3 U/mL) and not high (100 U/mL) concentrations of heparin. Among the available functional tests, SRA is the gold standard, but due to the use of radioactive substances and the complexity of the test, it is not generally used except in few reference laboratories[12,14]. According to most published data about HIT diagnosis in Iran[15-17], we came to this conclusion that the diagnosis of HIT in our country is almost always based on clinical evaluations (4Ts scoring system) due to the unavailability of laboratory assays (screening and confirmatory). The present study was thus conducted to determine the prevalence of HIT among patients with cardiac surgery using a comprehensive algorithmic approach to the diagnosis of HIT for the first time in Iran.

## MATERIALS AND METHODS

This single-center cross-sectional study was conducted at Modares Hospital in Tehran, Iran, over a period of 10 months.

During this time interval, any patient who was a candidate for cardiac surgery, e.g. coronary artery bypass grafting (CABG) and cardiac valve surgery (AVR and MVR), was included in this study. Their clinical information as well as the platelet counts during five to ten days after surgery was recorded.

The patients who did not consent to participation in this study or those with incomplete clinical data or patients who were discharged before ten days post-surgery were excluded from this study.

The patients' demographic data (age and gender), platelet count on the day of surgery and history of previous heparin exposure were recorded based on their medical records. The platelet counts were checked daily in the cardiac surgery ICU for 4-5 days and then every other day until ten days after surgery. Also, platelet counts were checked daily in the patients who received anticoagulant.

The 4Ts scoring system was used for evaluating the clinical probability of HIT in the patients on their last day of hospitalization.

A non-anticoagulated blood sample was collected from the patients with 4Ts scores ≥4. The patients'

specimens were sent to the special coagulation lab of the Iranian Blood Transfusion Organization (IBTO) for performing anti-PF4/heparin Ab testing by ELISA and HIPA tests. The serum samples were separated by the centrifugation of the specimens at 2500 g for 10 minutes and were stored at -70 °C until the testing.

**Laboratory tests**

1) Immunoassay: The ELISA method was used for detecting anti-PF4/heparin Abs of the IgG class (Asserachrom HPIA-IgG, Diagnostica STAGO) and OD >0.2 was considered positive based on the manufacturer's recommendations.

2) Functional test: The heparin-induced platelet aggregation (HIPA) test was used for the functional assay with the following details.

The patients' serum was incubated with washed platelets from four healthy donors (who had not taken any antiplatelet medications during the last ten days). A high concentration of heparin (100 IU/ml UFH), a low concentration of heparin (0.2 IU/ml Reviparin), and buffer and collagen were added to the micro-titer plate, respectively, with two steel spheres for 45 minutes at room temperature on a magnetic stirrer (1000 rpm) as the positive controls. The transparency of the suspension was checked every five minutes in indirect light. The result was considered positive when platelet aggregation occurred in the wells with a low concentration of heparin but not with a high concentration of heparin within 45 minutes[13].

**HIT definition**

HIT was taken as definite when a patient met the three following criteria together (Figure 1):

1) 4Ts score ≥4
2) Positive anti-PF4/heparin Ab by ELISA (OD>0.2).
3) Positive HIPA test.

This study was approved by the Ethics Committee of Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine.

**Statistical analysis**

The data obtained were analyzed in SPSS version 22 using the Chi-Square test and Mann-Whitney's U-test. $P<0.05$ was taken as the level of statistical significance.

**RESULTS**

During the study period, 100 patients were studied that 92 patients met eligible criteria for entering the study. These ninety-two patients underwent different kinds of cardiac surgery (CPB, CABG, AVR and or MVR, or combined procedures such as CABG+AVR or CABG+AVR+MVR). Fourteen of these 92 patients had 4Ts scores ≥4 (mean age: 62±11 years) Anti-PF4/heparin Ab was evaluated using the ELISA and HIPA tests in all the 14 patients. Eight cases showed positive ELISA (mean age: 58±11 years) and six cases (mean age: 66±2.1 years) showed positive HIPA test respectively (Table 2, and 3). According to the definition of HIT, five patients were taken as cases of HIT.

**DISCUSSION**

The present study was conducted on patients who had undergone different types of heart surgery over a 10 months period. Of the total of 92 patients under study, 14 (15%) had 4Ts scores ≥4 (maximum was 6). Of these 14 patients with 4Ts scores ≥4, only eight were ELISA positive, and only six out of these 14 patients were HIPA positive. Accordingly, HIT had occurred in five of the patients (5.4%) based on the three criteria noted in the algorithm used in this study.

The results of a retrospective study by Aguayo et al. on the national records of patients who had undergone heart surgery in 2009-2014 in the US showed that HIT had occurred in 0.4% of the 3,547,883 cardiac surgery patients. The incidence of HIT showed an increase with age, female gender, atrial fibrillation and heart failure, which are the independent risk factors of HIT[18]. Also, other studies showed that age is a risk factor of HIT[19, 20]. In this study, the mean age was 65 years (65±2.1) in the HIT positive group, while the mean age was 58 years (58±10.7) in the entire sample of patients. Warkentin et al. showed that women are at greater risk for HIT[21]. Although only 25 of the 92 patients

(27.1%) in this study were female, 50% of the patients with definite HIT were female and the mean antibody titers were higher in the female group than the male group (1.21 vs. 0.7). Since the number of patients in this study was low, we cannot conclude with certainty that increased age and female gender elevate the risk of HIT. Piednoir et al. examined the incidence of HIT in 1722 patients who had undergone heart surgery in one of the hospitals of Paris from 2005 to 2007 and reported the incidence of HIT as 3.6%. In their study, HIT was defined by: 1) The lack of other reasons for thrombocytopenia 2) ELISA positive results (>0.5 OD/mn) and 3) The recovery of platelet count after the discontinuation of heparin and its replacement with danaparoid sodium[22]. This definition is different from the definition provided in the present study for HIT, which may explain the small discrepancy between the findings of the two studies. Furthermore, the sample size of the present study was much smaller than that of Piednoir et al.'s study. Solanki et al. also examined the incidence of HIT in a review article and reported it as 0.1% to 5% in heart surgery. Their review also showed that some studies had reported an increase in the frequency of HIT with cardiopulmonary bypass [23]. The present study was different from the other studies in terms of sample size, duration of the study and the definition of HIT. HIT was defined in the present study as a 4Ts score ≥4, ELISA >0.2 and positive HIPA. Based on the diagnostic algorithm used in the present study, the incidence of HIT was about 5%, which is close to what Solanki et al. reported in their review study.

Few studies have been conducted on the incidence of HIT in Iranian patients undergoing heart surgery. Examples include two clinical trials on patients with HIT. Foroughinia et al. evaluated the incidence of HIT among 418 patients who had undergone different types of heart surgery and were being treated with UFH or low-molecular-weight heparin (LMWH) using the 4Ts scoring system. They reported that 17 patients (4%), including 11 receiving UFH and six receiving LMWH, had moderate to high risks of HIT[16]. Meanwhile, the frequency of patients with moderate to high 4Ts scores was 15% in the present study. Receiving UFH and LMWH is probably the reason for the difference between Foroughinia et al.'s study and the present study.

Beigmohamadi et al. performed a clinical trial on 564 patients who received high-dose heparin in the ICU and reported the incidence of HIT based on the 4Ts score and consultation with a hematologist as 15% (n=88), which is the same as in the present study[15]. Because they did not perform lab tests, it is not possible to compare the frequency of HIT incidence between their study and the present study based on a complete clinical laboratory algorithm. Another study conducted in Iran was the one by Motiee et al., who studied the incidence of HIT in 468 hospitalized patients who were receiving UFH or LMWH for the prevention or treatment of thrombosis. HIT incidence was assessed in this study by measuring the platelet count and performing SRA, and two of the 234 patients who had received UFH showed HIT[24]. This rate is much lower than the rate observed in the present study, which could be attributed to the different study population of our study, who were candidates for receiving heparin.

The most important point to consider about patients receiving heparin is that HIT should be promptly diagnosed and treated in them. Although HIT is not very prevalent, patients should be assessed for it daily, and if there is a risk for its development, lab tests should be used to confirm the diagnosis and start the treatment. The present study used an algorithmic approach mainly based on the 2013 American Society of Hematology guideline for the diagnosis and management of HIT, which is completely compatible with the latest ASH guideline published in 2018. According to the latest guideline, the first thing to do for patients receiving heparin is to determine their 4Ts score. Patients with moderate to high 4Ts scores (score: 4-8) are HIT suspected so all forms of heparin should be discontinued and non-heparin anticoagulant like Argatroban, Bivalirudin, Fondaparinux and Danaparoid should be started. Simultaneously these patients should undergo immunoassay and if the immunoassay turns out

positive, any available functional assays should be used. The 2018 guideline reports the sensitivity of functional assays such as HIPA as approximately 100%. This guideline diagnoses HIT step by step, helps save time and money and has a high sensitivity and specificity[5].

Farm et al. from Karolinska University also used a similar diagnostic algorithm for HIT. They first determined the 4Ts scores of the patients. Those who had moderate to high risks of developing HIT underwent immunoassay and those who were still suspected of HIT were tested by HIPA for a definite diagnosis. A five-year study of this algorithm revealed its high accuracy for the diagnosis of HIT. We also used an algorithmic approach for reaching a definite diagnosis of HIT.

Minet et al. carried out a review of the different diagnostic methods used for diagnosing HIT and investigated the sensitivity and specificity of functional assays. They aimed to find a rapid clinical lab functional test that was accessible, standard and rapid for diagnosing HIT and that was also economically and clinically feasible. They revealed that clinical labs use the following functional tests for diagnosing HIT: HIPA, C-SRA, Platelet Aggregation Test (PAT) and Heparin-Induced Multiple Electrode Aggregometry (HIMEA). Among these methods, HIPA had a high sensitivity and specificity. In addition, it needed less technical equipment, moderate work experience and acceptable duration compared to other functional[13]. In our study, we also used the HIPA test as a confirmatory method.

Nowadays, there are also several rapid immunoassays (RIs) for the fast primary diagnosis of HIT [25]. These tests are very useful in patients with a low or intermediate clinical probability, but the relatively significant rate of false negative results of RIs in patients with a high clinical risk (4Ts ≥ 6) needs to be considered, especially for revising diagnostic guidelines and the integration of RIs into the algorithm [26]. In the present study, RAs were not available in the center to allow for the better evaluation and the correct diagnosis.

## CONCLUSION

Since most of the studies conducted on HIT in Iran have not used a complete diagnostic panel for diagnosis; therefore, their results do not seem to indicate the actual prevalence of HIT and it seems that the rate of HIT is higher than 3% in this country. Given this rate and also the high expenses of ICU admission and the increased duration of treatment associated with this condition, accessible diagnostic methods and tests need to be developed for HIT in Iran. Given the high mortality associated with HIT and the heavy costs of the alternative treatments available for it, our health policymakers are recommended to develop a national guideline and assign at least one reference lab for HIT diagnosis in Iran. Our suggested protocol is performing a screening immunological antiPF4 Ab testing for each case with 4Tscore ≥4 and in the patients with positive screening test result, performing HIPA functional assay as the confirmatory test.

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### Study Limitations

This research was faced with several limitations. First, the sample size was small in comparison with the other studies. Second, calculating the 4Ts score in our study was based on the patient's documents; therefore, we cannot rule out the possibility of missing information, which could have affected the accurate calculation of the 4Ts score. Third, since this study was a student dissertation and had time and financial restrictions, we were unable to follow up on the patients for thrombotic events and other consequences beyond the ten-day follow-up period and also could not perform laboratory tests on all the eligible 92 patients.

**Table1.** 4Ts scoring system for evaluation of HIT clinical findings [8]

| Variable | 2 | 1 | 0 |
|---|---|---|---|
| Thrombocytopenia | >50% fall<br>nadir 20-100 × $10^9$/L | 30%-50% fall<br>nadir 10-19 × $10^9$/L | <30% fall<br>nadir < 10 × $10^9$/L |
| Timing of platelet count decrease | 5-10 days after exposure to heparin or day 1 in the recent heparin exposure | >day 10 after heparin exposure or unclear exposure | ≤day 4 with no recent heparin exposure |
| Thrombosis | New thrombosis<br>Acute systemic reaction anaphylactic reaction after heparin bolus | Progressive or recurrent thrombosis<br>Erythematous skin lesion at injection sites of heparin | No thrombosis |
| Other causes of Thrombocytopenia | None | Possible | Definite |

**Table 2**. Demographic data of the study population

| | Number of patients | Mean age (years) | Gender | |
|---|---|---|---|---|
| | | | Male | Female |
| Total | 92 | 58±10.7 | 67 | 25 |
| 4Ts scores <4 | 78 | 57±10 | 60 | 18 |
| 4Ts scores ≥4 | 14 | 62±11 | 7 | 7 |
| HIT positive | 5 | 65±2.1 | 3 | 2 |

**Table 3.** Details of 4Ts scores for fourteen patients with 4Ts scores ≥4

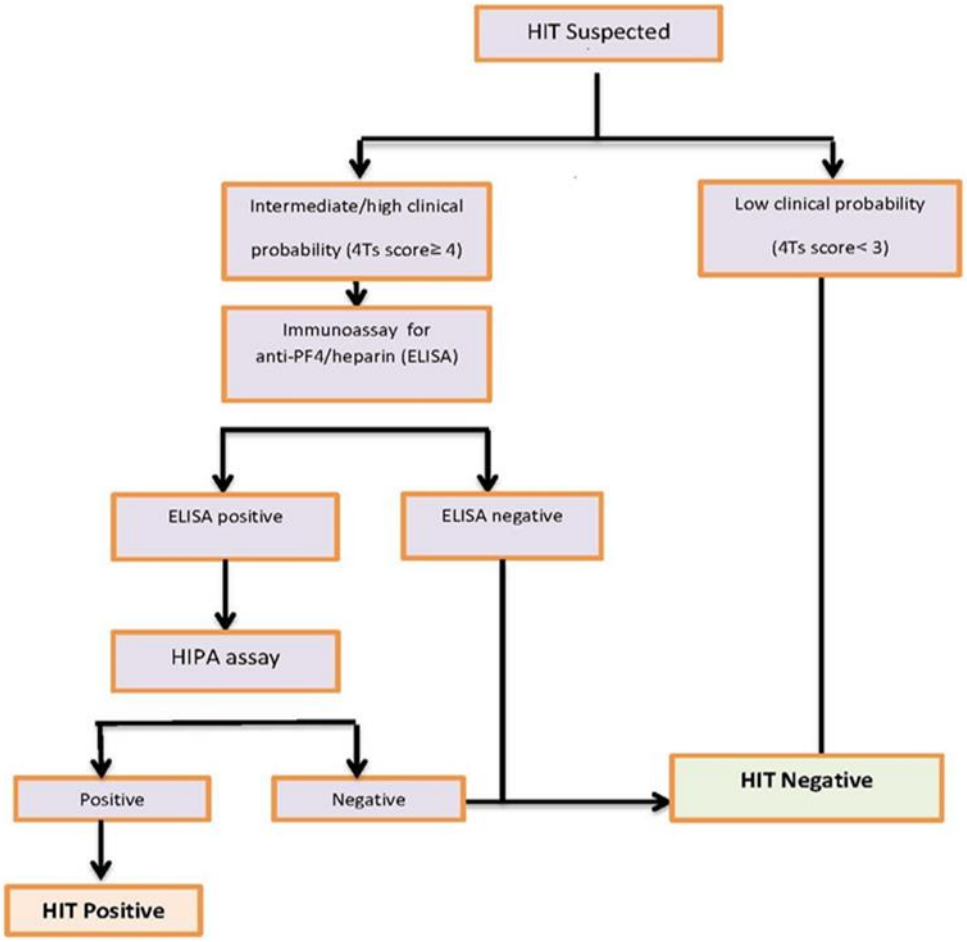
| Number of patient | Thrombocytopenia | Timing of platelet count decrease | Thrombosis | Other causes of thrombocytopenia | Total score |
|---|---|---|---|---|---|
| 1 | 2 | 2 | 0 | 1 | 5 |
| 2 | 1 | 2 | 0 | 2 | 5 |
| 3 | 2 | 2 | 0 | 1 | 5 |
| 4 | 2 | 0 | 0 | 2 | 4 |
| 5 | 2 | 2 | 0 | 2 | 6 |
| 6 | 2 | 2 | 0 | 2 | 6 |
| 7 | 1 | 1 | 0 | 2 | 4 |
| 8 | 2 | 1 | 1 | 2 | 6 |
| 9 | 1 | 2 | 0 | 1 | 4 |
| 10 | 2 | 2 | 1 | 1 | 6 |
| 11 | 2 | 2 | 0 | 2 | 6 |
| 12 | 2 | 2 | 0 | 1 | 5 |
| 13 | 1 | 2 | 0 | 2 | 5 |
| 14 | 2 | 2 | 0 | 0 | 4 |

**Table 4**. Demographic characteristics, 4Ts scores and laboratory test results of the 14 patients with 4Ts scores ≥4

| Patient number | Gender (F/M) | Age (year) | 4Ts Score | ELISA (Positive.: OD>0.2) | HIPA Test | Definite HIT |
|---|---|---|---|---|---|---|
| 1 | F | 64 | 5 | 0.617 | Positive | + |
| 2 | M | 63 | 5 | 0.470 | Positive | + |
| 3 | M | 66 | 5 | 0.286 | Positive | + |
| 4 | F | 33 | 4 | 0.327 | Negative | – |
| 5 | F | 61 | 5 | 1.028 | Positive | + |
| 6 | M | 72 | 6 | 1.088 | Positive | + |
| 7 | F | 57 | 5 | 1.803 | Negative | – |
| 8 | M | 51 | 5 | 0.277 | Negative | – |
| 9 | M | 67 | 4 | 0.144 | Negative | – |
| 10 | F | 72 | 4 | 0.154 | Positive | – |
| 11 | F | 72 | 6 | 0.160 | Negative | – |
| 12 | M | 55 | 6 | 0.103 | Negative | – |
| 13 | M | 81 | 5 | 0.149 | Negative | – |
| 14 | F | 63 | 4 | 0.108 | Negative | – |

F: Female, M: Male

The positive ELISA and HIPA tests showed in italic




Algorithm 1-Diagnostic Algorithm for HIT

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