Evaluation of pretest clinical score (4 T’s) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings

G. K. LO,* 1 D. JUHL,* 1 T. E. WARKENTIN,* † C. S. SIGOUIN,* 1 P. EICHLER† and A. GREINACHER†

Department of Medicine, McMaster University, Hamilton, ON, Canada; †Department of Immunology and Transfusion Medicine, Ernst-Moritz-Arndt University, Greifswald, Germany; and †Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada


See also Aster RH. Heparin-induced immune thrombocytopenia – a clinical or laboratory diagnosis? This issue, pp 757–8.

Summary. Background: Heparin-induced thrombocytopenia (HIT) is a prothrombotic adverse drug reaction caused by heparin. As thrombocytopenia is common in hospitalized patients receiving heparin, it would be useful to have a clinical scoring system that could differentiate patients with HIT from those with other reasons for thrombocytopenia. Aim: To compare prospectively the diagnostic utility of a clinical score for HIT in two different clinical settings. Methods: The pretest clinical scoring system, the ‘4 T’s’, was used to classify 100 consecutive patients referred for possible HIT in one hospital (Hamilton General Hospital, HGH) into high, intermediate, and low probability groups. This system was also used to classify likewise 236 patients by clinicians in Germany referring blood for diagnostic testing for HIT in Greifswald (GW). The clinical scores were correlated with the results of laboratory testing for HIT antibodies using the serologic criteria for HIT with high diagnostic specificity. Results: In both centers, patients with low scores were unlikely to test positive for HIT antibodies [HGH: 1/64 (1.6%), GW: 0/55 (0%)]. Patients with intermediate [HGH: 8/28 (28.6%), GW: 11/139 (7.9%)] or high scores [HGH: 8/8 (100%), GW: 9/42 (21.4%)] were more likely to test positive for clinically significant HIT antibodies. The positive predictive value of an intermediate or high clinical score for clinically significant HIT antibodies was higher at one center (HGH). Conclusions: A low pretest clinical score for HIT seems to be suitable for ruling out HIT in most situations (high-negative predictive value). The implications of an intermediate or high score vary in different clinical settings.

Keywords: heparin, scoring system, thrombocytopenia.

Introduction

Heparin can cause a prothrombotic adverse effect known as heparin-induced thrombocytopenia (HIT) [1,2]. Given the ubiquity of heparin use, HIT is one of the most common immune-mediated adverse drug reactions, with frequencies as high as 2–3% for certain groups of postoperative patients and 0.5–1% for general medical patients receiving unfractionated heparin (UFH) for a week or more [3–5].

However, there are several potential explanations for thrombocytopenia in a patient receiving heparin besides HIT. Although there are sensitive assays available to detect pathogenic HIT antibodies, major limitations remain. Firstly, test results are not always available in a timely fashion. Secondly, the tests often detect non-pathogenic antibodies [6–8], causing diagnostic uncertainty. Moreover, the decision to stop heparin, or to substitute heparin with an alternative anticoagulant, can be problematic. For example, simply stopping heparin in a patient with HIT is frequently complicated by thrombosis [8–10]. Conversely, substituting heparin with an alternative anticoagulant, such as lepirudin or argatroban, in a patient who does not have HIT is expensive and could be associated with major bleeding in up to 10–20% of patients because of their potent antithrombin effect [11,12].

Based on these considerations, it could be useful to have a clinical scoring system that has a high-negative or -positive predictive value (or, ideally, both) for diagnosis of HIT. Here, we provide evidence that a clinical scoring system yielding a low score has high-negative predictive value in assessing patients with suspected HIT.

Methods

Patients and study design

Our study included patients evaluated for thrombocytopenia or suspected HIT in two clinical settings. In the first setting, the
scoring system was applied to inpatients at the Hamilton General Hospital (HGH), a tertiary care center in Canada. One hundred consecutive inpatients were assessed over a 17-month period independently by two physicians. The evaluations were conducted prospectively by a physician (T.E.W.) who frequently assesses patients referred for possible HIT (or in whom a diagnosis of HIT was entertained during a consultation for thrombocytopenia and/or thrombosis), and retrospectively by an internal medicine/hematology resident (G.K.L.) by means of chart review using information up to (and including) the date of the initial consultation.

In the second clinical setting, physicians of various specialties working in a variety of healthcare settings throughout Germany and Austria applied the scoring system and submitted their assessments as a component of the requisition form for ordering testing for HIT antibodies. These data were collected over a 9-month period by the HIT testing laboratory in Greifswald (GW), Germany. Other data recorded in both clinical settings were: underlying disease, duration of heparin, baseline platelet count at start of heparin, platelet count at time of serological testing, presence of sepsis, and other concomitant illnesses. The study was approved by the local ethical review boards of both institutions.

Clinical model

The scoring system employed (4 T’s) is shown in Table 1, with minor modifications [13,14]. There were minor differences between the two scoring systems used in HGH and GW (see Table 1 footnote). The scoring system evolved from previous systems [15–18] that were usually developed to assess new diagnostic testing for HIT antibodies. The clinical features used to develop the scoring system were derived from the typical clinical features of HIT, including the magnitude of the fall in platelet count [19,20], the timing of the thrombocytopenia relative to heparin exposures [21,22], the strong association with thrombosis [19,20], including skin lesions at heparin injection sites [23] and the presence or absence of an alternative diagnosis [19]. The resulting clinical probability scores were divided into high (6–8 points), intermediate (4–5 points), and low (≤3 points) groups. The rationale for setting a high score at 6 or more points was based empirically upon the consideration that a patient who did not have clinical evidence of thrombosis but who fulfilled all other clinical features of HIT would score 6 points, thus providing strong justification for the administration of an alternative (non-heparin) anticoagulant.

Hamilton diagnostic techniques

Blood samples for testing for HIT antibodies were obtained at the time of hematology consultation. The tests were performed at a central laboratory by observers unaware of the patients’ clinical information. Detection of HIT antibodies was conducted by means of the platelet serotonin release assay (SRA) [24,25] and a commercial PF4/polyanion-enzyme immunoassay (EIA) available from Genetic Testing Institute (GTI) Inc. (GTI-PF4; GTI Inc., Brookfield, WI, USA) [26]. We considered the following cutoffs as indicating a ‘positive’ result: SRA, ≥20% serotonin release; GTI-EIA > 0.40 OD (optical density) units. However, given the high frequency of subclinical seroconversion in patients receiving heparin, we considered a priori clinically significant HIT antibodies to be those that caused ≥50% serotonin release and that tested positive for anti-PF4/heparin antibodies by EIA. These criteria were used...
because prospective studies indicate that a positive SRA of this magnitude has a strong association with clinical HIT (odds ratio, about 10–25), and is observed in more than 90% of patients with clinical HIT; in contrast, relatively few patients (<10%) with a weak-positive result (20–49.9% serotonin release) evince clinical HIT [27,28]. In addition, we tested the patients with a low score and positive EIA-GTI for anti-PF4/heparin antibodies of IgG class [29]. If a serum tested indeterminate using the SRA (i.e. serotonin release occurred at all concentrations of heparin) [30], then we considered the sample as indicating a high likelihood of HIT if anti-PF4/heparin antibodies of IgG class were detected with optical density >1.0 OD units [8].

Greifswald diagnostic techniques

The heparin-induced platelet activation (HIPA) test was considered positive if at least three of four donor platelets showed activation in the presence of a low (0.2 U mL\(^{-1}\)), but not a high (100 U mL\(^{-1}\)) heparin concentration, with a lag time of 30 min or less, and all the control wells reacting as expected [31–33]. Weakly-reacting sera (30–45 min lag time) were considered negative. The immunoassay used was an in-house EIA that detects anti-PF4/heparin antibodies of all three major immunoglobulin classes, IgG, IgM, and IgA, with a cutoff of 0.7 OD units. We considered, as positive for clinically significant HIT antibodies, those patients who tested positive in both assays. Patients with a low score who tested positive by the screening EIA were also tested for anti-PF4/heparin antibodies of IgG class.

Data analysis

Overall differences between the incidence of clinically significant HIT antibodies and the three clinical score categories were assessed using a 2 × 3 chi-squared analysis. Differences between sites and the incidence of clinically significant HIT antibodies within each clinical score category were assessed using a Fisher’s exact test.

The inter-observer reliability of the model, which was assessed at the HGH site, was determined by a weighted kappa test (95% CI). Where differences in scoring occurred between the two investigators in HGH, the results presented were those based upon the score assigned by the senior investigator (T.E.W.).

All P-values were based on the two-tailed tests and the level of statistical significance was set at \( P < 0.05 \). The SAS System for Windows Release 8.2 was used to conduct the analyses.

Pre hoc ranges

To be considered a successful scoring system, both the HGH and GW groups determined in advance the acceptable ranges for low and high pretest probability. A ‘low’ pretest score should have a strong positive HIT assay result in <5%, and a ‘high’ pretest score should give a similar strong positive result in at least 50% of patients.

Results

Table 2a (HGH) and b (GW) summarizes the types of patients assessed for HIT in relation to the clinical score. In both settings, at least 80% of patients investigated for HIT were derived from one of the three patient categories: cardiovascular surgery, internal medicine, and intensive care (although the relative proportions differed somewhat). Notably, orthopedic surgery patients (a patient group previously reported to have a high frequency of HIT) were infrequently investigated for HIT. Table 3a (HGH) and b (GW) summarizes HIT antibody test results in relation to the clinical scores, whereas Table 4a and b summarizes those patients with a low clinical score who tested at least weakly positive in one or both assays for HIT antibodies.

Hamilton

Table 3a shows the results of 100 consecutive inpatients referred to the hematology service who were evaluated using the scoring system. Sixty-four of the patients scored in the ‘low’ probability category, of whom only one (1.6%) tested positive for clinically significant HIT antibodies. Twenty-eight patients scored in the ‘intermediate’ pretest probability category, of

<table>
<thead>
<tr>
<th>Pretest category</th>
<th>Cardiovascular surgery</th>
<th>Internal medicine</th>
<th>Intensive care</th>
<th>General surgery</th>
<th>Neurology/neurosurgery</th>
<th>Orthopedic surgery</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Low</td>
<td>30</td>
<td>13</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>Intermediate</td>
<td>15</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>28</td>
</tr>
<tr>
<td>High</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Total (%)</td>
<td>50 (50.0%)</td>
<td>20 (20.0%)</td>
<td>10 (10.0%)</td>
<td>7 (7.0%)</td>
<td>9 (9.0%)</td>
<td>4 (4.0%)</td>
<td>100 (100%)</td>
</tr>
<tr>
<td>(b) Low</td>
<td>5</td>
<td>23</td>
<td>11</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>45*</td>
</tr>
<tr>
<td>Intermediate</td>
<td>26</td>
<td>63</td>
<td>29</td>
<td>11</td>
<td>1</td>
<td>2</td>
<td>132*</td>
</tr>
<tr>
<td>High</td>
<td>8</td>
<td>17</td>
<td>3</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>41*</td>
</tr>
<tr>
<td>Total (%)</td>
<td>39 (17.9)</td>
<td>103 (47.2)</td>
<td>43 (19.7)</td>
<td>24 (11.0)</td>
<td>6 (2.8)</td>
<td>3 (1.4)</td>
<td>218 (100%)</td>
</tr>
</tbody>
</table>

*Excludes 18 patients for which information regarding patient type was not available.
whom eight (28.6%) had clinically significant HIT antibodies. All eight (100%) patients who scored in the ‘high’ pretest probability group tested positive for clinically significant HIT antibodies. The difference in incidence of clinically significant HIT antibodies in the three categories was statistically significant \((P < 0.0001)\). The weighted kappa value for the assessment of inter-observer reliability for the clinical model was 0.84 (95% CI, 0.75, 0.94).

In the one patient classified as having a low clinical score who tested positive for clinically important HIT antibodies (Patient 1 in Table 4a), the SRA was strongly positive (93% serotonin release) and the GTI-EIA was also strongly positive (2.126 OD units). This patient, who was subsequently shown to have antiphospholipid antibodies, developed a rapid fall in platelet count starting the day when heparin was given to treat spontaneous arterial thrombi affecting the cerebral arteries and distal aorta that led to her admission to hospital (no previous heparin exposure was identified). This atypical clinical presentation perhaps reflects an unusual feature of her underlying autoimmune disease, with autoantibodies reactive against PF4/heparin.

Ten (15.6%) of the 64 patients who were classified as having a low clinical score tested negative or weakly-reactive in the functional HIT assay (SRA) (Patients 2–11 in Table 4a). Nine of these were positive only in the EIA-GTI (one with an indeterminate SRA). Seven of these nine patients had anti-PF4/heparin antibodies of IgG class. One patient had a positive EIA-GTI and a weakly-positive SRA (25% release). These 10 patients, as well as the single patient with a low clinical score who tested positive for clinically significant HIT antibodies, are summarized in Table 3a. In all cases, the clinical information indicated an alternative diagnosis besides HIT as a plausible explanation for the thrombocytopenia. Furthermore, only one patient developed subsequent thrombosis (asymptomatic upper-limb superficial venous thrombosis).

### Greifswald

During the 9-month study period, 304 samples were referred to GW for diagnostic HIT testing. Of the 304 test requisition forms, 68 did not have the clinical score assessed, leaving 236 evaluable scores for analysis. Table 3b shows the results. Fifty-five (23.3%) patients had a low clinical score, 139 (58.9%) had an intermediate clinical score, and 42 (17.8%) had a high clinical score. None of the patients with a low score tested positive in the HIPA test, but four tested positive in the PF4/heparin-EIA (Table 4b); only one of these four patients had anti-PF4/heparin antibodies of IgG class. In all four of these patients, an alternative, non-HIT explanation for the thrombocytopenia was readily apparent. In the intermediate score group, 11 (7.9%) of 139 patients, and in the high score group, nine (21.4%) of 42 patients tested positive for clinically significant HIT antibodies (as defined \(a\ priori\)), with an increasing percentage of positive testing among patients with higher scores.

### Discussion

We found that the negative predictive value of the HIT score was high in both clinical settings. In HGH, one of 64 (1.6%) patients who had a low clinical score tested positive for clinically significant HIT antibodies, as defined \(a\ priori\). In GW, none of the 55 patients who had a low clinical score tested positive for clinically significant HIT antibodies. Both thus met the predetermined value of <5%. This indicates that the clinical score has the potentially useful property of predicting which patients are most unlikely to have a serological profile indicating the presence of HIT.
In contrast to the high-negative predictive value of the clinical scoring system, we found that the positive predictive value differed considerably in the two clinical settings. Whereas in HGH, all eight (100%) patients with a high score tested positive for clinically significant HIT antibodies, this was not observed in GW, where only nine (21.4%) of 42 patients tested positive for clinically significant antibodies (P < 0.0001 by Fisher’s exact test, two-sided). A similar pattern was observed in the patients with an intermediate clinical score: among these patients, the frequency of having a positive test for clinically significant antibodies (≥0.60) was greater in HGH than in GW: 8/11 (73%) versus 9/42 (21.4%) patients tested positive for clinically significant HIT antibodies. This result is consistent with the findings of recent studies suggesting that the positive predictive value of HIT testing ordered for patients with a high clinical score is lower in GW than in HGH [35,36].

There are several potential explanations for these differences. In our opinion, the most likely explanation is the clinical experience of the clinician in applying the scoring system. In HGH, the scoring system was utilized by only two investigators (one of whom developed the scoring system) to 100 consecutive patients. In contrast, the clinical score was used by numerous physicians in GW, each of whom would have developed minimal experience using the scoring system. Another potential explanation could be differences in the frequency of HIT between these two clinical settings. Notably, although UFH is still widely used in North America, low-molecular-weight heparin (with its lower frequency of HIT [3,19,34]) has undergone wider acceptance and use in Europe [3,34]. Thus, a scoring system could exhibit a lower-positive predictive value simply because the frequency of HIT is relatively low, and thus the relative proportion of HIT-mimicking thrombocytopenic disorders [35], for example, platelet count decrease associated with fulminant pulmonary embolism or sepsis in a patient who has received heparin is relatively high. It is also possible that the minor differences in the scoring systems used could explain the part of the differences in the data obtained, although this seems unlikely.

In keeping with our finding that the positive predictive value can differ considerably in different evaluative settings, recent reports assessing this clinical scoring system also reflect such variability. For example, a group of independent investigators [36] that evaluated the 4 T’s scoring system among postcardiac surgery patients (a population at relatively high risk of HIT [3,5]) observed the high-positive predictive value among patients with a high (11/11 = 100%) or intermediate

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(24/53 = 45.3%) score. In contrast, the 4 T’s had a low-positive predictive value among pediatric patients (a low-risk group) evaluated for HIT in another study [37].

In HGH, 10 (15.6%) of 64 patients with a low clinical score tested positive for anti-PF4/heparin antibodies by EIA together with a weak or negative SRA. In GW, the corresponding values (with negative HIPA) were four (7.3%) of 55 patients. In all of these patients, a non-HIT explanation for thrombocytopenia was readily apparent (Table 4a and b). The rationale for our a priori decision to consider a ‘weak’ positive assay (such as a positive EIA with a negative or weak-positive SRA [20–49.9% serotonin release]) as not being indicative of clinical HIT was based upon our previous studies [19,27,28,38,39] of blood obtained from patients in prospective studies of heparin therapy in which we found that ‘strong’ platelet-activating antibodies (≥250% serotonin release) are identified in at least 90% of patients with clinical HIT; in contrast, the great majority of patients with weak antibodies do not develop clinical HIT. The patient populations examined in these previous studies – postorthopedic and postcardiac surgery patients – represent groups in which ‘late’ platelet count falls that begin on or after day 5 have relatively few explanations besides HIT [19,34], thus providing valuable information on the operating characteristics (sensitivity–specificity tradeoffs) of these assays.

Our present study infers that there is the potential for considerable over-diagnosis of HIT, if any single ‘positive’ test (especially the EIA) is assumed to ‘confirm’ the diagnosis of HIT, particularly in a clinical setting of low pretest probability for HIT (i.e. a low clinical score). For example, if among the HGH patients we were to consider HIT to be present in any patient with at least a moderate or high clinical score who also tested positive for clinically significant HIT antibodies (as we defined a priori), then 16 (16.0%) of the 100 patients would have met this clinico-pathologic definition combining both clinical and laboratory criteria. In contrast, if patients with a low clinical score and ‘weak’ positive testing (defined above) were considered to have had HIT, then an additional 10 patients would have been diagnosed (incorrectly in our view) as having had HIT. Given that few medical centers perform platelet activation assays for HIT, and that blood specimen referral to reference centers capable of performing platelet activation assays probably occurs infrequently, our study suggests that one way to reduce over-diagnosis of HIT is to limit serological investigations in most situations to patients with an intermediate or high clinical score.

It is becoming more common to treat patients suspected as having HIT with an alternative non-heparin anticoagulant. Our findings suggest that this could be an appropriate approach for patients with a moderate or high clinical pretest probability, at least in some clinical settings. However, this might not be the optimal approach for patients with low pretest probabilities, as the frequency of HIT in this subgroup is small (< 2%) compared with the risk of major bleeding complications associated with the use of alternative anticoagulants (10–20%). Thus, in patients with low clinical scores, especially if not complicated by thrombosis, maintenance of heparin may be a more appropriate, and potentially safer, option. While this must be confirmed by an appropriate clinical trial or cohort study, our data suggest that serological investigations for HIT antibodies can be omitted in these patients. As a large proportion of patients (65% in HGH, 23% in GW) has a low clinical score, and thus a low pretest probability for HIT, costs of HIT antibody testing may be reduced by limiting testing of patients to those with intermediate or high clinical scores.

In conclusion, the use of a clinical model for assessing the pretest probability of HIT has the potential to simplify and improve the process of identifying patients at different risk of HIT. In particular, low pretest clinical scores for HIT are suitable for ruling out HIT in most clinical settings. Prospective studies will be required to test the clinical utility and safety of this or any other clinical model in guiding the management of HIT.

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