



Improved prediction of HIT in the SICU using an improved model of the Warkentin 4-T system: 3-T

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ABSTRACT

Background: The Warkentin 4-T scoring system for determining the pretest probability of heparin-induced thrombocytopenia (HIT) has been shown to be inaccurate in the ICU and does not take into account body mass index (BMI).

Methods: Prospectively collected data on patients in the surgical and cardiac ICU between January 2007 and February 2016 who were presumed to have HIT by clinical suspicion were reviewed. Patients were categorized into 3 BMI groups and assigned scores: Normal weight, overweight, and obese. Multivariate analyses were used to identify independent predictors of HIT.

Results: A total of 523 patients met inclusion criteria. Multivariate analysis showed that only BMI, Timing, and other variables were independently associated with HIT. This new 3-T model was better than a five-component model consisting of the entire 4-T scoring system plus BMI (AUC = 0.791).

Conclusions: Incorporating patient Thickness into a pretest probability model along with platelet Timing and the exclusion of other causes of thrombocytopenia yields a simplified “3-T” scoring system that has increased predictive accuracy in the ICU.

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Background

Heparin-induced thrombocytopenia, type II (HIT), is a potentially life-threatening, immune-mediated disease clinically characterized by thrombocytopenia, disseminated intravascular coagulation, thrombocytopenia, venous or arterial thrombosis, skin necrosis, and anaphylactoid reactions.¹ The pathophysiology of HIT involves a type 2 antibody-mediated hypersensitivity reaction against macromolecular complexes formed electrostatically between the cationic alpha granule protein platelet factor 4 (PF4) and anionic unfractionated heparin.² Autoantibodies against the heparin-PF4 complex activate both innate and adaptive immune

responses, leading to platelet consumption and consumptive coagulopathy.³ Prompt recognition of the disease is required in order to prevent and manage serious sequelae, including thrombosis and death. Treatment consists of immediate cessation of heparin therapy, treatment with non-heparin anticoagulants, and close surveillance for the development of thrombosis.⁴ To date, however, there is no single test that is adequate for recognition of the disease. Rapid immunoassays used to detect anti-PF4 antibodies are a sensitive but nonspecific test for HIT. Whereas antibodies against the complex are necessary for development of HIT, 8–17% of medical and surgical patients treated with heparin and 27–61% of cardiac surgery patients will develop detectable PF4 titers, but the rates of HIT are orders of magnitude lower.^{5–10} Conversely, functional platelet assays are far more specific for HIT but are labor and resource intensive, generally requiring the sample be sent to a reference lab with a delayed result that returns outside the window of clinical decision making.¹¹

In many centers, the diagnosis of HIT is currently done with a three stage Bayesian screening and testing process. In the first step,

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the Warkentin 4-T score is used to determine the pretest probability of identifying HIT by assigning 0–2 points for relative values in four categories, including magnitude of thrombocytopenia, timing of thrombocytopenia relative to heparin exposure, presence of thrombosis, and probability of other causes of thrombocytopenia.¹² In patients with a low pretest probability for HIT (≤ 3 points), no further workup is indicated. In patients with an intermediate-to-high pretest probability (≥ 4 points), the sensitive anti-PF4 immunoassay is then used to quantify levels of PF4 antibodies, which can immediately rule out or strongly suggest a strong posttest probability of HIT.¹³ As a final step, the time, labor, and cost intensive functional C14 serotonin release assay is then used in confirmatory testing.¹⁴

The ultimate accuracy of the diagnosis of HIT is the product of the accuracy of the individual screening and testing steps. Improvement in the accuracy of the initial clinical scoring system would prevent missed diagnoses and eliminate unnecessary costs by avoiding superfluous testing. It has been shown that the commonly used Warkentin 4-T scoring system has diminished accuracy in the ICU setting.¹⁵

Several studies have found a significant correlation between obesity and either a greater prevalence or a worse prognosis of many immune-mediated diseases, such as rheumatoid arthritis¹⁶, systemic lupus erythematosus¹⁷, inflammatory bowel disease¹⁸, multiple sclerosis¹⁹, Type –1 diabetes¹⁸, psoriasis²⁰, and Hashimoto's thyroiditis²¹. Obese patients may experience a state of chronic subclinical inflammation, resulting in an increased incidence of various comorbidities, especially related to cardiovascular diseases.^{22–24} Our previous work discovered an association between increasing BMI and increased rates of HIT, mean anti-PF4 levels and SRA% in ICU patients, and suggested that BMI was a factor independent of the 4T system.²⁵ This paper follows on the previous work to incorporate BMI as an independent variable in an improved scoring system.

Methods

An institutional database with data on all patients with a clinical suspicion of HIT prompting laboratory evaluation or consult by the inpatient hematology service was prospectively collected. All patients in the surgical/trauma and cardiac surgery intensive care units with data collected between January 2007 and February 2016 were included for analysis. Demographic and clinical data including patient age, sex, height, weight, Warkentin 4-T scores including

individual component sub-scores, and serotonin release assay (SRA) were analyzed by an expert in coagulation pathology. Patients with SRA $>20\%$ were considered positive for HIT. Patients were categorized into 3 BMI groups: normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), or obese (≥ 30.0 kg/m²). For inclusion of BMI in a composite risk score, increasingly large BMI groups were awarded 0, 1 or 2 points for BMI 18.5–24.9, 25–29.9, ≥ 30 ; similar to the Warkentin scoring system, and the 2-sided Cochran-Armitage Trend Test was used to confirm an ordered association between serially increasing BMI groups and the incidence of HIT. Multivariate analyses were used to identify the independent predictors of HIT. Receiver operating characteristic (ROC) curves were evaluated to compare the accuracy of multiple predictive models.

Results

A total of 523 patients met inclusion criteria. Summary demographic and clinical data are presented in Table 1. The mean BMI was 27.0 ± 6.2 kg/m². Forty-nine (9%) patients were considered positive for HIT based on a positive SRA. Examining the association between HIT and BMI, we found that the incidence of HIT increased progressively with BMI [normal weight, 6.6%; overweight, 7.8%; obese, 15.3%; $p = 0.008$]. To maintain symmetry with the 4-T system, we assigned increasing values (0, 1, 2) to the ascending BMI classes, and to keep with the 4-T acronym to make it easier to recall, we substitute patient “T” hickness as a synonym for BMI.

We next sought to determine which of the components of the 4-T scoring system were associated with HIT. Among the 4-T scoring components, on univariate analysis only the scores for the timing of thrombocytopenia relative to heparin administration ($p < 0.001$) and the likelihood of other causes of thrombocytopenia were associated with diagnosis of HIT by SRA ($p < 0.001$). Scores corresponding to the magnitude of thrombocytopenia and presence of thrombosis were not associated with HIT diagnosis. The total 4-T score $p < 0.001$ was also significantly associated with a positive SRA.

In order to determine whether BMI could add information to the scoring system, we performed multiple logistic regression for the diagnosis of HIT including BMI and individual 4-T score components. In multivariate analysis, BMI [aOR = 4.19, 95% CI = 1.48–12.9, $p = 0.025$]; timing of thrombocytopenia [aOR = 2.37, 95% CI = 1.26–4.53, $p = 0.007$]; and other causes of thrombocytopenia [aOR = 3.96, 95% CI = 1.09–8.90, $P < 0.001$] were independently

Table 1
Patient demographics. Continuous variables are reported as mean \pm SD. BMI and 4-T score differ significantly in the HIT positive SICU population.

Variable	Total (n = 523)	HIT Positive (n = 49)	p-value
Demographics			
Age, yrs	60.3 \pm 15.9	58.1 \pm 15.1	0.338
Sex			
Male	63% (327)	10% ³³	0.537
Female	37% (196)	8.1% ¹⁶	
BMI (kg/m²)			
18.5–24.9	40.5% (212)	9.37% (49)	0.017
25–29.9	32.9% (172)	6.6% ¹⁴	
≥ 30	26.6% (139)	8.7% ¹⁵	
		14.4% ²⁰	
4-T score			
(0–3)	72.7% (380)	3.4% ¹³	<0.001
4,5	19.3% (101)	17.8% ¹⁸	
6–8	8.0% (42)	42.9% ¹⁸	

associated with HIT. As this suggested that BMI provided additional information in assessing likelihood of HIT, we compared ROC curves of the traditional 4-T model and our new 3-T model using only the factors we identified as significantly associated with HIT (BMI, timing of thrombocytopenia, and other causes of thrombocytopenia). The limited model (AUC 0.85) had significantly improved receiver characteristics than the full 4-T scoring system (AUC 0.77). Adding BMI to the full 4-T scoring system did not significantly improve accuracy (AUC 0.79) relative to the parsimonious model. These results suggest that a simplified scoring model utilizing scores for BMI, timing of thrombocytopenia, and likelihood of other causes of thrombocytopenia could be more accurate in the ICU setting.

Discussion

In the multistage diagnosis of HIT, improvement in the accuracy of the clinical scoring system used to determine pretest probability can help prevent missed diagnoses as well prevent overutilization of expensive and labor-intensive tests. For patients in the surgical ICU, the Warkentin 4-T system has diminished accuracy and a different scoring system may provide better results.¹⁵ Previous attempts at adding obesity to the 4-T score did not yield a model with increased predictive value.²⁶ We demonstrated that a new minimal model consisting of BMI plus two of the 4-T scoring components—the timing of thrombocytopenia and the likelihood of other causes—yields a simpler three-component scoring system that has improved predictive accuracy for patients in surgical critical care units.

The addition of BMI to the scoring system adds a potentially etiologic element to an otherwise clinically descriptive scoring system. Recent work from our group and others have demonstrated that obesity is an independent risk factor for HIT.^{25,27} Furthermore, obesity is known to contribute to a hypercoagulable state and platelet hyperaggregability due to increased estrogen production.^{28,29} It is unclear whether this effect is due to the proinflammatory and proimmunogenic state accompanying obesity that is associated with a number of comorbidities such as metabolic syndrome, insulin resistance and type II diabetes,³⁰ or if there is a specific effect on platelets from associated soluble factors such as leptin, which is known to enhance platelet aggregation.^{31–33} Additional biochemical work is required to further decipher the mechanistic basis of the association between obesity and HIT. Identification of additional etiologic factors in addition in obesity may further improve clinical screening and assessment of pretest probability when the diagnosis of HIT is being considered.

These results have several limitations. First, as a retrospective analysis of a single institutional database, these findings require validation in an independent cohort for confirmation. Furthermore, the cohort examined is not representative of the whole surgical/trauma and cardiac surgery ICU population, as the database included only patients undergoing workup for HIT. Such patients already have generated clinical suspicion for HIT, which leads to a self-selection bias. Conversely, patients for whom there was clinical suspicion but low 4-T scores who did not undergo testing were not included, which may impact the generalizability of these findings. In addition, there is some clinically relevant heterogeneity in the patient population examined. Rates of HIT and PF4 testing characteristics are different for patients who have sustained trauma or undergone cardiac surgery with cardiopulmonary bypass.^{34,35} Given the relatively low incidence of HIT to begin with, it is difficult to perform subcohort analysis for heterogeneity in these patient populations.

Unlike many institutions we have a special coagulation consultative service within the department of Pathology. Several years ago we developed a HIT task force in collaboration with the Pharmacy department to reduce cost for unnecessary treatments with PF4 and SRA assays. A Pathologist with expertise in coagulation reviews each HIT order and PF4 results and applies the 4T scoring system to the case. For every borderline positive or positive PF4 IgG, an SRA is sent out to a commercial laboratory. If the SRA results are negative, but there is strong clinical suspicion (high 4T) the PF4 and SRA are repeated in 1–2 days. For this study, every 4T score was analyzed by an expert in coagulation. These may be slightly different from the scores, if any were applied, calculated by resident, fellow or ordering physician.

For those cases that have a low probability score to begin with, a HIT workup should not be ordered. The current reality is that sometimes the clinical suspicion for HIT is triggered by thrombocytopenia, without the application of full 4T score. As we have shown, thrombocytopenia per se does not have strong association with HIT. In our practice we have encountered several HIT cases with borderline PF4 > 0.4 < 1.0 OD scores and intermediate HIT probability, that indeed were HIT. Therefore, the decision was made to send an SRA on every positive antiPF4 with OD > 1.0.

HIT, although a rare diagnosis, requires vigilance and prompt diagnosis to prevent serious sequelae. Improvement in clinical scoring systems assessing the pretest probability of HIT will aid in risk stratification and efficient allocation of resources. The new 3-T model presented here improves upon the widely used current 4-T model for stratifying the pretest probabilities of HIT in the surgical critical care population (see Tables 2–4).

Table 2
Odds Ratios for the Development of HIT, per point. Timing of platelet count fall, exclusion of other potential causes, and increased patient BMI are statistically significant indicators of increased risk of HIT.

Variable	Adjusted Odd Ratio
4-T Thrombocytopenia	0.54 [0.13–3.20]; p = 0.80
4-T Timing	2.57 [1.32–5.20]; p < 0.01
4-T Thrombosis	1.20 [0.33–3.99]; p = 0.77
4-T oTher	3.74 [1.76–8.61]; p < 0.01
Patient Thickness (BMI)	2.64 [1.39–8.51]; p < 0.01

Table 3
3-T Scoring System: Patient thickness is stratified by BMI into normal weight, overweight, and obese categories. The point assignments for timing of platelet fall and exclusion of other causes retain identical scoring to the Warkentin 4-T model.

Variable	0 points	1 point	2 points
Patient Thickness (BMI)	18.5–24.9 kg/m ²	25–29.9 kg/m ²	>30 kg/m ²
Timing	<4 days	Onset > day 10	5–10 days
oTher	definite	possible	none

Table 4
Comparison of Accuracy of Different Scoring Systems: The 3-T model has superior accuracy compared to the 4-T model and the 4-T plus BMI model in SICU patients.

System	AUC
4-T score	0.77
Patient Thickness (BMI) + 4-T score	0.79
Patient Thickness (BMI) + Timing + oTher	0.85

Conflicts of interest

The authors declare no conflicts of interest.

Disclosures

The authors have no relevant disclosures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjsurg.2019.07.039>.

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