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Results: PF4 tests were requested in 643 patients based on a clinical suspicion of HIT. Of those, 104 patients had a PF4 result, a SRA value (%), and a 4-T Score available. Twenty patients (19%) had true positive HIT, defined as a positive PF4 (PF4 ≥ 0.4 OD) and positive SRA (SRA ≥ 21%). 84 patients (81%) were False Positives, defined as a positive PF4 and negative SRA.

Conclusions: Although a PF4 ≥ 0.4 OD is considered a positive screening test for HIT, a PF4 ≥ 2.0 OD is more predictive of true positive HIT in surgical ICU patients. Current guidelines, which are based primarily on medicine patients, overtreat surgical ICU patients. New guidelines need to be established to prevent the overdiagnosis of HIT in surgical ICU patients.
Overdiagnosis of Heparin-induced thrombocytopenia (HIT) in surgical ICU patients

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INTRODUCTION

Venous thromboembolism (VTE) is a common complication for patients undergoing operations, and pulmonary embolism (PE) is the most common cause of preventable death in patients hospitalized for surgical procedures.\(^1\)\(^2\) In patients undergoing general surgery without prophylaxis, the rates of deep vein thrombosis (DVT) and fatal PE range from 15% to 30% and from 0.2% to 0.9%, respectively.\(^1\)\(^3\) Prophylaxis with either low-dose unfractionated Heparin (LDUH) and low-molecular-weight Heparin (LMWH) have been shown to reduce the risk of VTE in surgical patients by at least 60%.\(^2\)\(^4\) The American College of Chest Physicians (ACCP) 2008 guidelines\(^5\) state that for moderate-risk general surgery patients who are undergoing a major procedure for benign disease, thromboprophylaxis with LMWH, LDUH twice daily (three times daily in high risk patients), or fondaparinux is recommended.

Heparin use in surgical patients places them at increased risk for developing Heparin-induced thrombocytopenia (HIT). HIT is an acquired, transient, antibody mediated thrombocytopenia which occurs in a subset of patients and is caused by Heparin exposure that confers a high risk of venous and arterial thrombosis. Once the diagnosis of HIT is suspected, the American Society of Hematology recommends\(^14\) the discontinuation of heparin, administration of a non-Heparin anticoagulant (Lepirudin, Argatroban, or Bivalirudin), and HIT confirmation with a serological assay (Figure 1). Two groups of serological assays are available: immunologic tests used as screening assays and functional tests, used as confirmatory assays. Immunologic tests such as the Platelet Factor 4 (PF4) ELISA detect antibodies against PF4/Heparin complexes. Functional tests such as the Serotonin Releasing Assay (SRA) detect IgG antibodies that induce Heparin-dependent platelet activation. Controversy exists in accurately diagnosing HIT in complex severely ill surgical ICU patients. In ICU patients, the
diagnosis and treatment of HIT is especially problematic as HIT affects <1% of ICU patients even though 30–50% develop thrombocytopenia.\textsuperscript{15}

Treatment of HIT often begins once the screening assay is positive (PF4 ≥ 0.4 as defined by the manufacturers) which involves significant changes in management; places post-operative surgical patients at increased risk of bleeding compared to medical patients by utilizing alternative anticoagulants recommended by the current clinical guidelines; and increases costs. Therefore, accurate diagnosis of HIT is critical. As the current guidelines are based primarily on general medicine patients, the false positive rate of HIT using the above criteria is unknown in surgical ICU patients who often have confounding factors such as sepsis, resuscitative hemodilution, or liver disease which place them at increased risk for the development of thrombocytopenia and thrombosis. Thus, the purpose of this study is to determine the value of PF4 and Warkentin 4-T Score associated with the development of HIT as defined by SRA ≥ 21%, in surgical ICU patients.

\textbf{METHODS}

This is a retrospective study of patients admitted to the Surgical Intensive Care Unit of an urban, academic medical center. All patients presumed to have HIT by clinical criteria and who had a positive PF4 ELISA screening test between January 2008 and February 2010 were included in the study. The clinical diagnosis of HIT was made using the Warkentin 4-T Scoring system\textsuperscript{16} (Table 1) which is based on four features: Thrombocytopenia; Timing of thrombocytopenia; Thrombosis; and an alternative cause. Each feature is allotted 0 to 2 points and a subsequent score of 0–8 points is generated. If the score is 0–3, HIT is unlikely. A score of 4–5 indicates an
intermediate suspicion of HIT, while a score of 6–8 makes HIT highly likely.\textsuperscript{15-18} A PF4 test was considered positive for HIT for values \( \geq 0.4 \) Optical Density [OD] (as recommended by GTI Diagnostics’ PF4 Enhanced\textsuperscript{®} Solid Phase ELISA Manufacturers). Confirmation of HIT was made with a \(^{14}\text{C}\) Serotonin Releasing Assay (SRA), run by Quest Diagnostics and the Blood Center of Wisconsin (after 2008). Values \( \geq 21\% \) were considered positive for HIT.

Patient characteristics (age, sex, race, Acute Physiology and Chronic Health Evaluation [APACHE] II Score, Simplified Acute Physiology Score [SAPS], type of surgery, and type of heparin exposure) and outcomes (ICU length of stay [LOS], hospital LOS, mortality, and thrombosis) were recorded and evaluated. Data regarding the PF4 values, Warkentin 4-T Score, and SRA were also documented. Patients with SRA \( \geq 21\% \) were classified as true positive (TP) for HIT while patients with SRA < 21\% were classified as HIT false positives (FP). Only patients with PF4 \( \geq 0.4 \) were included in this study, therefore no true negatives were included for analysis. Comparisons of patient characteristics and outcomes were made between the TP group and FP group.

Categorical variables were compared by the Fisher exact test. Numerical variables were compared by the t test (normal distribution) or the Wilcoxon rank sum test (non-normal distribution). Logistic regression was used to determine the relationship between independent risk factors and the development of HIT. Odds ratios (OR), as well as their 95\% confidence intervals, were calculated. \( P < 0.05 \) was used to determine significance. All statistical analysis was performed using SAS, version 9.1 (SAS Institute, Cary, North Carolina). This study received institutional review board approval.
RESULTS

Based on a clinical suspicion of HIT, PF4 ELISA tests were requested for 643 surgical ICU patients and 137 of those patients were positive (PF4 ≥ 0.4 OD). Of the 137 patients, 104 patients had a PF4 value, a SRA value, and a Warkentin 4-T Score. Twenty patients (19%) were TP HIT and 84 patients (81%) were FP HIT. Forty-two percent of the sample population had undergone cardiothoracic surgery while 49% of patients were post-operative general surgery, trauma surgery, neurosurgery, vascular surgery, kidney transplant, and urology patients. Thirteen surgical ICU patients had undergone central line placement (Table 2). In comparing TP to FP, FP patients were more critically ill with significantly higher APACHE II and SAP score. The PF4 value for the TP group was significantly higher (2.23 OD ± 0.96 vs. 0.98 OD ± 0.65, P < 0.0001) (Table 2). As expected, the SRA value and the Warkentin 4-T Score for TP were significantly higher when compared to FP. Figure 2 shows HIT results for increasing Warkentin score. With an intermediate suspicion for HIT (Warkentin Score 4-5), 23 patients were FP and 9 patients were TP. A Warkentin score of 6-8 (high suspicion for HIT) resulted in 8 FP patients and 6 TP patients. Figure 3 shows HIT results for increasing PF4 ELISA OD. Eighty-four PF4 tests were ordered based on a clinical suspicion for HIT. Values ranging from 0.4 to 1.99 OD resulted in only 7 TP patients. For PF4 values above 2.0 OD, 13 were TP and 7 were FP. There were no significant differences in ICU LOS, hospital LOS, and mortality between the TP and FP groups, respectively (Table 3). Thrombosis was noted in all TP patients with deep vein thrombosis representing the most common type. Table 4 demonstrates the odds ratios for developing HIT in patients with a PF4 ≥ 0.4 OD. When compared to patients with a Warkentin 4-T Score of 0-3, the group of patients with a Warkentin 4-T Score of 4-5 had 4.15 times the
odds of developing HIT and those with a Warkentin 4-T Score of 6-8 had 7.95 times the odds of developing HIT.

Treatment consisted of either discontinuing Heparin with no further treatment or discontinuing Heparin with the subsequent commencement of direct thrombin inhibitors Argatroban or Lepirudin. In evaluating the total sample population, Heparin was discontinued in 59.6% of patients with no further treatment whereas 31.7% were further treated with Argatroban or Lepirudin. Heparin was not discontinued in 8.7% of patients. When comparing TP to FP, Heparin was discontinued with the subsequent commencement of either Argatroban or Lepirudin in 23% of the FP group and in 65% of the TP group.

DISCUSSION

Heparin Induced Thrombocytopenia (HIT) is an acquired, transient, anti-coagulant-induced, antibody mediated thrombocytopenia caused by Heparin exposure that confers a high risk of venous (causing deep vein thrombosis, pulmonary embolism, and adrenal hemorrhagic infarction) and arterial thrombosis (causing myocardial infarction and/or stroke, skin necrosis, and limb ischemia). Heparin binds to a protein known as PF4 causing the immune system to develop antibodies (usually IgG) against this complex usually within 5 to 10 days of the Heparin exposure. The antibody then binds to the Fc receptor, found on the surface of platelets, causing their activation. Activation of platelets results in platelet consumption and thrombocytopenia in addition to the formation of platelet-derived procoagulant microparticles resulting in thrombosis.
HIT is classified into two types: non-immune mediated (Type I) and immune-mediated (Type II). Type I occurs in approximately 10-30% of patients exposed to UFH. Mild thrombocytopenia typically develops within 1-2 days of UFH exposure and normalizes despite continued Heparin exposure. No significant adverse clinical events have been associated with Type I. Type II results from an adverse drug reaction caused by Heparin-dependent antibodies (usually IgG) that activate platelets/endothelial cells. Although less common (1-5% incidence) than Type I, Type II is more severe as it results in a high risk of thrombotic events.

In determining Type II onset, Battistelli and colleagues describe three variants: Typical-onset HIT, Rapid-onset HIT, and Delayed-onset HIT. Typical-onset HIT is the most common variant and occurs 5-10 days after the initiation of Heparin in 70% of patients. Rapid-onset HIT occurs in 25-30% of patients and can appear within 24 hours of Heparin treatment. Delayed-onset HIT occurs several days to weeks after the discontinuation of Heparin in 5% of patients.

The ACCP Evidence-Based Clinical Practice Guidelines (Eighth Edition) recommend investigating for a diagnosis of HIT if the platelet count drops by 50% and/or a thrombotic event occurs between 5 and 14 days following the initiation of Heparin, even if the patient was no longer receiving Heparin therapy when the thrombosis or thrombocytopenia occurred. One year following the publication of ACCP recommendations, the American Society of Hematology published diagnostic clinical guidelines adapted from the ACCP guidelines which included the initial treatment algorithm (adapted) for the management of HIT, published by Arepally in 2006 (Figure 1). The ACCP current clinical guidelines recommend treatment of patients suspected of having HIT with non-Heparin anticoagulants (Lepirudin, Argatroban, or Bivalirudin) in place of UFH or LMWH, prior to HIT confirmation with the SRA. Based on the
results from this study, only 19% of the study population had a positive PF4 screening test and a positive SRA test and thus had TP HIT. Yet per the current guidelines, 81% (FP group) met the criteria for the discontinuation of Heparin followed by the commencement of a non-Heparin anticoagulant.

The overall incidence of HIT varies from 0.1% to 5%; however the incidence differs between medical and surgical patients. Girolami et al evaluated 598 hospitalized medical patients treated with subcutaneous unfractionated Heparin (UFH) and determined the incidence to be 0.1%-1.6%. In contrast, Warkentin et al evaluated 744 post-operative orthopedic and cardiac surgery patients treated with Heparin and found the frequency of HIT-IgG formation to range from 3.2% in orthopedic patients receiving low molecular weight heparin to 20% in cardiac surgery patients receiving UFH. Thus, surgical patients are at an increased risk for the development of HIT when compared to medical patients.  

While 42% of our sample population represented cardiothoracic patients, 45% of these were FP for HIT. The diagnosis of HIT in postoperative cardiac surgery patients remains challenging as hemodilution and platelet consumption during cardiopulmonary bypass can result in a 40%-60% drop in platelets on post-operative day 2 and 3. In addition, during the first 10 days post-cardiac surgery, 25–70% of patients develop anti-PF4–Heparin antibodies detectable by immunoassays, and 4–20% test positive by platelet activation assay; yet only a few of these patients develop clinically evident HIT. Despite the large percentage of cardiothoracic patients in the current study, 49% of the study population were post-operative general surgery, neurosurgery, trauma, urology, vascular, or were surgical ICU patients who had undergone placement of a central line.
Like post-operative cardiac surgery patients, the diagnosis of HIT in surgical ICU patients can also be challenging as an alternative explanation for or the etiology of thrombocytopenia could include sepsis, peri-operative and post-resuscitation hemodilution, drug-induced thrombocytopenia, massive transfusion, liver disease, platelet consumption or destruction, or disseminated intravascular coagulation. In fact, in the current study, patients who had a higher severity of illness as assessed by APACHE II and SAP scores were more likely to be diagnosed as FP when compared to TP.

For the analysis in this paper some patients were initially categorized as ‘Indeterminate’ HIT. We defined ‘Indeterminate’ HIT as a PF4 $\geq 0.4$ OD, SRA $< 21\%$, and a Warkentin 4-T Score of $\geq 4-8$ (intermediate/high clinical probability of HIT). Three patients initially had SRA values $<21\%$; however, due to high 4-T score and elevated PF4 values, SRA tests were repeated. In one patient, the SRA increased from 10% to 75% within 4 days of repeating the test. In another patient, the SRA rose from 0% to 31% to 86% within 3 days of the initial test. Both patients were classified as TP. A third patient had an initial SRA value of 0. Upon repeat testing in 14 days, the SRA value had increased to 52%. However, the SRA test was evaluated again 3 days later and the value decreased to 19%; thus, this patient was classified as FP. Another patient had an initial SRA value of 17%; however, when the same specimen was sent to a different laboratory, the SRA value was 97% and so the patient was classified as TP. Two patients within the study were classified as FP because the SRA values were $<21\%$ but they had an intermediate clinical probability of HIT based on the Warkentin 4-T score, PF4 $> 0.8$ OD, and deep vein thrombosis. However, the SRA confirmatory test was negative. There were 11 patients who remained ‘Indeterminate’ but were analyzed as FP because their SRA were $<21\%$. Management and treatment of these patients can prove to be challenging and must rely on
clinical judgment until specific guidelines can be established in the surgical ICU patient population.

Current guidelines\(^{14}\) recommend treating patients with an intermediate suspicion of HIT (Warkentin Score of at least 4) with non-Heparin anticoagulants prior to HIT confirmation with the SRA; however, we found 31 patients (30\%) with an intermediate to high clinical suspicion for HIT were still FP. In critically ill patients, the Warkentin 4-T scoring system\(^{16}\) lacks specificity and this study is best used in the ICU to assist in ruling out HIT for a 4-T score <4, while an intermediate to high score (≥ 4) necessitates more specific testing.\(^{15}\) In reviewing the literature, the SRA test has high sensitivity (>95\%) and high specificity (>99\%). In a prospective clinical trial by Warkentin\(^{47}\), a strong-positive SRA result (defined as >50\% serotonin release at pharmacologic Heparin concentrations) was associated with a high likelihood of clinical HIT [odds ratio (OR) = 78.2; P < 0.001]. However, the high sensitivity and low specificity of PF4 ELISA screening tests are known limitations. Warkentin\(^{39}\) et al commented that many patients exposed to Heparin develop anti-PF4/Heparin antibodies detectable by the PF4 ELISA test in the absence of clinical HIT which could lead to a false diagnosis of HIT in a Heparin-exposed patient in whom the explanation for thrombocytopenia is another condition. Warkentin\(^{40}\) et al provide two reasons for the low diagnostic specificity of the PF4 ELISA test. First, the cutoff values in OD units that define a positive test result are determined using blood obtained from normal individuals who have not been exposed to Heparin. In contrast, diagnostic testing is almost always performed in patients who have been exposed to Heparin. Thus, the background OD distribution of Heparin-exposed patients without HIT could differ considerably from the distribution of normal individuals. Secondly, not all antibodies detectable by the PF4 ELISA test have the biological properties needed to effect platelet activation. Lo\(^{41}\) et al further explain
Warkentin’s second observation by stating that many patients form non-activating antibodies of IgM or IgA class, or non- or only weakly platelet-activating antibodies of IgG class, and thus do not develop HIT. Warkentin et al propose that the solution to this dilemma is to either raise the diagnostic PF4 cut-off threshold or establish a range of PF4 values which indicate varying probabilities of clinical HIT.

A PF4 ≥ 0.4 OD is considered to be a positive screening test by the manufacturers’ recommendations. We found that the PF4 value for the TP group was significantly higher when compared to the FP group. However, when 84 PF4 tests were ordered based on a clinical suspicion for HIT, only 7 of 84 patients were TP for the test with values ranging from 0.4 to 1.99 OD. Of the 20 PF4 tests above 2.0 OD, 13 were TP. Given the higher observed incidence of HIT above 2.0 OD, if PF4 level is ≥2.0 OD then a more aggressive HIT management with non-Heparin anticoagulants might be considered prior to SRA availability, although this method was correct only 65% of the time.

Treatment of HIT with non-Heparin anti-coagulant direct thrombin inhibitors (i.e. Argatroban, Lepirudin, and Bivalirudin) places post-operative surgical patients at an increased risk for bleeding when compared to medical patients. In our study, 23% of the FP patients and 65% of the TP HIT patients were treated with either Argatroban or Lepirudin. Extreme caution is necessary in the use of Argatroban in patients after major surgery due to the risk of bleeding and the difficulty with reversing this anticoagulant. Two prospective, multicenter, nonrandomized studies (ARG 911 and ARG-915) evaluated the efficacy and safety of Argatroban, as an anticoagulant, in patients with HIT and found that when compared to controls bleeding rates were the same. However, both studies did not specifically evaluate post-operative surgical patients in both arms of the study. In fact, in the ARG-915 study, 12 patients were
withdrawn from the treatment arm because of surgery. Lepirudin, however, has been associated with an increased risk of bleeding and may precipitate anti-Lepirudin antibody formation. Three prospective, multicenter nonrandomized trials (HAT 1, HAT 2, and HAT 3)\textsuperscript{46-48} found that major bleeding was more frequent in the Lepirudin-treated patients (29.4\% vs. 9.1\%, \(P=0.0148\)). For patients with HIT requiring cardiac surgery, two prospective, open label, multicenter trials, CHOOSE-ON\textsuperscript{49} and CHOOSE-OFF\textsuperscript{50}, concluded that Bivalirudin is the preferred DTI for intraoperative anticoagulation. As with Argatroban and Lepirudin, Bivalirudin also increases the risk of bleeding as 84\% of patients in the CHOOSE-ON trial received transfusions before day 7 or discharge with a mean of 5.6 units of packed red blood cells and 8.6 units of platelets. In addition to the increased risk of bleeding, the estimated cost per day for Bivalirudin is $533, $884 for Argatroban, and $1759 for Lepirudin.\textsuperscript{51} Thus, the accurate diagnosis of HIT in the surgical patient is critical.

Our findings indicate the current algorithm for HIT diagnosis and treatment in critically ill surgical patients should not follow the recommended guidelines (Figure 1) as 81\% of the surgical ICU patients in our study with a clinical suspicion for HIT were false positive and could have been potentially treated with Argatroban or Lepirudin. The Warkentin 4-T Score should be used as an initial step to calculate the clinical probability of HIT. However, from our results, management should not depend solely on the Warkentin 4-T as there were 5 patients with a 4-T score of \(< 4\) who were true positive HIT, and 8 patients who were false positive HIT with a 4-T score of 6-8. If there is clinical suspicion of HIT based on the Warkentin 4-T Score, the PF4 screening test should be ordered with the SRA confirmatory test. Based on our results, if the PF4 was less than 2.0 OD then the chance of TP was 8\% and if the PF4 was above 2.0 OD, TP rate increased to 65\%. As such, in critically ill surgical patients, acute treatment may be initially
ruled out for PF4 below 2.0 OD while awaiting SRA results. For PF \( \geq 2.0 \) a direct thrombin inhibitor may be considered, although 35% of these patients will not require this therapeutic. When possible, HIT diagnosis and treatment in the ICU population should depend on the results of the SRA confirmatory test as this test is currently considered the gold standard. As presented, when repeat SRA confirmatory tests were available they were often variable; the accuracy of this test may require further analysis in critically ill surgical patients.

There are a number of limitations to our study. As in all retrospective database studies, the design of the database used for data analysis limits the conclusions that can be established. The results are representative of a single institution’s experience. Thirty-three patients were excluded because of missing data for either SRA values or a Warkentin 4-T Score, introducing a certain level of bias to the study. In addition, the small sample size weakened the power of the study as well as the ability to include PF4 levels in the logistic regression analysis. To address the above mentioned limitations, a large multicenter, retrospective/observational trial is needed to corroborate our findings and establish specific clinical guidelines for the management of HIT in post-operative surgical patients.

In conclusion, only 19% of surgical ICU patients in our study with a diagnosis for HIT based on current PF4 guidelines were true positive. Although a PF4 \( \geq 0.4 \) OD is considered a positive screening test for HIT, a PF4 \( \geq 2.0 \) OD is more predictive of true positive HIT with a true positive rate of 65%. Current guidelines, which are based primarily on medicine patients, overtreat surgical ICU patients.
REFERENCES


<table>
<thead>
<tr>
<th>4Ts Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Point</th>
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</thead>
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<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>Platelet count fall &gt; 50% from baseline AND platelet nadir ≥ 20 x 10^9/L</td>
<td>Platelet count fall 30% to 50% from baseline OR platelet nadir 10-19 x 10^9/L</td>
<td>Platelet count fall &lt; 30% from baseline OR platelet nadir &lt; 10 x 10^9/L</td>
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<tr>
<td><strong>Timing of platelet count fall</strong></td>
<td>Clear onset between days 5 and 10 OR platelet fall ≤ 1 day with Heparin exposure within 30 prior days</td>
<td>Fall in platelet counts consistent with onset between days 5 and 10 but timing is not clear due to missing platelet counts OR onset after day 10 of Heparin exposure OR fall in platelet counts ≤ 1 day with prior Heparin exposure between 30 and 100 days prior</td>
<td>Platelet count fall &lt; 4 days without recent Heparin exposure</td>
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<td><strong>Thrombosis or other sequelae</strong></td>
<td>New thrombosis, skin necrosis, or acute systemic reaction after unfractionated Heparin exposure</td>
<td>Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis</td>
<td>No thrombosis or thrombosis preceding Heparin exposure</td>
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<td><strong>Other causes of thrombocytopenia</strong></td>
<td>None apparent</td>
<td>Possible other causes present</td>
<td>Probable other causes present</td>
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The 4Ts score is assigned by summing the values for each of the 4 categories. A score of 1, 2, or 3 is considered low clinical suspicion; 4 or 5 is considered intermediate clinical suspicion; and 6,7, or 8 is considered high clinical suspicion. Reproduced with permission.
FIGURE 1. American Society of Hematology Diagnostic & initial treatment algorithm\textsuperscript{14,39}

- **HIT Suspected**
  - Intermediate/High Clinical Probability
    - Discontinue Heparin and start non-heparin anticoagulant
      - Obtain Immunologic Assay (PF4)
        - Positive
          - Obtain Functional Assay (SRA)
            - Positive
              - HIT Likely
            - Negative
              - HIT Indeterminate
        - Negative
          - High Clinical Probability
            - Negative Intermediate Clinical Probability
              - HIT Unlikely; continue Heparin; consider alternative diagnosis
  - Low Clinical Probability

\textsuperscript{14,39}
### TABLE 2. Characteristics of Study Population

<table>
<thead>
<tr>
<th></th>
<th>Total Sample (N=104)</th>
<th>True Positives (N=20)</th>
<th>False Positives (N=84)</th>
<th>P-Value</th>
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<tr>
<td>Age in years</td>
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<td>61.0 ± 18.7</td>
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<td>Male n (%)</td>
<td>67 (64.4)</td>
<td>13 (65.0)</td>
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<td>Race n (%)</td>
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<tr>
<td>Other</td>
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<td>1 (1.2)</td>
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<td>APACHE II</td>
<td>22.0 ± 10.5</td>
<td>17.7 ± 10.4</td>
<td>23.1 ± 10.4</td>
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<td>SAPS</td>
<td>15.4 ± 6.4</td>
<td>12.9 ± 7.4</td>
<td>16.0 ± 6.1</td>
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<td>Type of surgery n (%)</td>
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<td>Cardiothoracic</td>
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<td>6 (30.0)</td>
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<td>17 (16.4)</td>
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<td>14 (16.7)</td>
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<td>None</td>
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<td></td>
</tr>
<tr>
<td>Central Line Placement</td>
<td>13 (12.5)</td>
<td>5 (25.0)</td>
<td>8 (9.5)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>4 (3.8)</td>
<td>3 (15.0)</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Urology</td>
<td>1 (1.0)</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Vascular</td>
<td>4 (3.8)</td>
<td>0 (0)</td>
<td>4 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Heparin Exposure n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Drip</td>
<td>19 (18.3)</td>
<td>4 (20.0)</td>
<td>15 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Flush</td>
<td>18 (17.3)</td>
<td>3 (15.0)</td>
<td>15 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>57 (54.8)</td>
<td>9 (45.0)</td>
<td>48 (57.1)</td>
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</tr>
<tr>
<td>Unknown</td>
<td>10 (9.6)</td>
<td>4 (20.0)</td>
<td>6 (7.1)</td>
<td></td>
</tr>
<tr>
<td>PF4 [OD]</td>
<td>1.22 ± 0.87</td>
<td>2.23 ± 0.96</td>
<td>0.98 ± 0.65</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SRA [%]</td>
<td>14.0 ± 27.4</td>
<td>65.2 ± 24.0</td>
<td>1.9 ± 4.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Warkentin 4-T Score</td>
<td>3.2 ± 2.1</td>
<td>4.7 ± 2.2</td>
<td>2.9 ± 1.9</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

Age, APACHE II, SAPS, PF4, SRA, and Warkentin 4-T results are reported as mean ± standard deviation.
FIGURE 2. HIT results for increasing Warkentin Score

![Bar chart showing HIT results for increasing Warkentin Score. The chart categorizes the number of tests into three ranges: 0 to 3, 4 to 5, and 6 to 8, with the number of true positives and false positives indicated for each range.]
FIGURE 3. HIT results for increasing PF4 ELISA OD

![Bar chart showing the number of tests for different PF4 ELISA OD ranges, with categories for True Positive and False Positive.
### TABLE 3. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Total Sample (N=104)</th>
<th>True Positives (N=20)</th>
<th>False Positives (N=84)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU LOS in days</td>
<td>23.5 ± 30.9</td>
<td>23.9 ± 29.8</td>
<td>23.4 ± 31.3</td>
<td>0.85</td>
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<tr>
<td>Hospital LOS in days</td>
<td>38.1 ± 39.1</td>
<td>36.0 ± 30.4</td>
<td>38.6 ± 41.0</td>
<td>0.82</td>
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<tr>
<td>Mortality, n (%)</td>
<td>39 (37.5)</td>
<td>7 (35.0)</td>
<td>32 (38.1)</td>
<td>0.80</td>
</tr>
</tbody>
</table>

LOS—Length of Stay; ICU LOS and Hospital LOS are reported as mean ± standard deviation.
<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years),</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 year increase</td>
<td>1.00</td>
<td>0.97 – 1.03</td>
<td>0.86</td>
</tr>
<tr>
<td>Per 5 year increase</td>
<td>1.01</td>
<td>0.88 – 1.17</td>
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<tr>
<td>Sex, Female vs. Male</td>
<td>0.97</td>
<td>0.35 – 2.69</td>
<td>0.95</td>
</tr>
<tr>
<td>APACHE II,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 point increase</td>
<td>0.94</td>
<td>0.89 – 1.00</td>
<td>0.053</td>
</tr>
<tr>
<td>Per 5 point increase</td>
<td>0.74</td>
<td>0.55 – 1.01</td>
<td></td>
</tr>
<tr>
<td>SAPS,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per 1 point increase</td>
<td>0.92</td>
<td>0.84 – 1.01</td>
<td>0.065</td>
</tr>
<tr>
<td>Per 5 point increase</td>
<td>0.66</td>
<td>0.43 – 1.03</td>
<td></td>
</tr>
<tr>
<td>Warkentin 4-T Score: 0-3</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warkentin 4-T Score: 4-5</td>
<td>4.15</td>
<td>1.25 – 13.74</td>
<td>0.020</td>
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<tr>
<td>Warkentin 4-T Score: 6-8</td>
<td>7.95</td>
<td>1.96 – 32.25</td>
<td>0.004</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS.

1. **FIGURE 2:** HIT results, grouped by Warkentin Score (0-3: HIT unlikely; 4-5: intermediate suspicion; 6-8 high suspicion) (X-axis), from 104 Warkentin tests ordered (Y-axis) based on a clinical suspicion of HIT. True Positive--Patients with SRA ≥ 21%, False positive--Patients with a SRA < 21%. Reproduced with permission.

2. **FIGURE 3:** HIT results, grouped by 0.4 Optical Density [OD] (X-Axis), from 104 PF4 ELISA tests ordered (Y-axis) based on a clinical suspicion of HIT. True Positive--Patients with SRA ≥ 21%, False Positive--Patients with a SRA < 21%.