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Impact of Platelet Functional Assays on the Cost of Treating Suspected Heparin-Induced Thrombocytopenia

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Abstract

Objectives: To investigate the potential cost savings of using functional platelet assays to confirm the diagnosis of heparin-induced thrombocytopenia (HIT). *Methods:* This was a single-center study conducted in the United States. We performed a retrospective cost of illness analysis of suspected HIT, comparing patients with the serotonin release assay (SRA) ordered as part of their diagnostic evaluation to those who did not. The primary clinical end point was a composite of mortality and major bleed. *Results:* A total of 147 patients met the study's inclusion criteria. An SRA was ordered in 53 patients of whom 17% were positive. Overall, SRA use did not reduce the composite primary clinical end point (32.1% vs 33%, $P = .911$). Also, there was no difference in the total cost of hospital stay (US $84781.1 vs US $78534.4, $P = .409$) nor in the direct medical costs related to HIT management (US $7473.5 vs US $8402.4, $P = .393$). Early ordering of the SRA (within 48 hours) was associated with shorter length of stay (20 vs 27 days, $P = .029$) but without a difference in cost of treatment. *Conclusion:* The use of SRA did not reduce the costs or improve clinical outcomes in patients with suspected HIT.

Keywords

cost of illness, direct thrombin inhibitor, heparin, thrombocytopenia, thrombosis

Introduction

Immune-mediated heparin-induced thrombocytopenia (HIT type II) is a rare complication that affects 0.2% to 5% of all patients exposed to heparin products and results from the formation of antibodies directed against the heparin/platelet factor 4 (PF4) complex. These antibodies activate platelets and produce a hypercoagulable state that can subsequently lead to an increased risk of thrombosis (30%-75%), occurring in both the venous and the arterial vasculature.[1,2] Even when managed with alternative anticoagulants, HIT can be associated with a dramatic increase in mortality.[3]

Prompt diagnosis and management of HIT are key to minimize the risk of life-threatening thrombosis. However, diagnosis of this syndrome is challenging and requires correlation between clinical symptoms and laboratory assays. Measurements of platelet function, such as the serotonin release assay (SRA), are considered the gold standard diagnostic laboratory tests due to their ability to detect the underlying hypercoagulable state in patients with true HIT. Although the specificity and sensitivity of these tests are over 90%, they are very technically demanding to perform and therefore are not widely available at most institutions.[4,5]

The more widely available immunologic assays, including the PF4 enzyme-linked immunosorbent assay (ELISA), are the most common methods for screening patients for HIT. However, despite their high sensitivity (>95%), immunologic assays have a relatively low specificity (50%-89%), leading to a high rate of false positives. The use of optical density (OD), among other methods, was proposed as a way to increase ELISA specificity.[6,7] Similarly, clinical scoring systems, specifically the 4Ts score, have been used as a tool to identify patients at low risk of HIT, with a negative predictive value of 91% with the ELISA.[8]

HIT imposes a significant economic burden on the health care system. Pharmacoecomnomics studies have shown that the development of HIT is associated with an increased length

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of stay, as well as an increase in cost of hospitalization.[9-14] Previous studies performed in the United States have estimated the overall cost of management of HIT. However, these studies did not evaluate the potential cost implications of incorporating a functional assay in the diagnosis of HIT nor the costs of treating false-positive HIT (ie, false-positive ELISA screening). As a result of the relatively high false-positive rate associated with immunologic screening, a significant number of patients may be exposed to unnecessary diagnostics and drug treatment for HIT, which could increase their length of stay and augment the overall economic burden of suspected HIT.

The purpose of this study was to estimate the costs associated with the diagnosis and treatment of suspected HIT and to explore how the use of functional platelet assays might affect both the clinical outcomes and the overall costs of this disorder.

Study Methods

This study is a cost-of-illness analysis of suspected HIT from the health system perspective, conducted at Henry Ford Hospital, an 802-bed, tertiary care, level 1 trauma center in Detroit, Michigan. This study was approved by the hospital's institutional review board. Data were collected retrospectively from patients diagnosed with suspected HIT between January 2007 and October 2011. Suspected HIT was defined as thrombocytopenia necessitating heparin discontinuation, positive ELISA, and initiation of an alternative anticoagulant. Thrombocytopenia was defined as a platelet count less than 150 000/μL or a 50% or more reduction in platelets from baseline following 5 to 10 days of heparin or low-molecular-weight heparin therapy (or within 24 hours in patients with recent exposure to heparin products). Based on our institutional guidelines, patients with HIT were started on either argatroban or lepirudin upon diagnosis of suspected HIT. Argatroban was reserved for those patients with renal dysfunction or those with previous exposure to lepirudin. The direct thrombin inhibitors (DTIs) and warfarin dosing were managed by a Pharmacist Directed Anticoagulation Service (PDAS), as directed by a collaborative practice agreement. Warfarin was initiated once platelet count recovered, then overlapped with the DTI for a minimum of 5 days and until international normalized ratio is within the target range. At the time of data collection, the PDAS comprised 5 pharmacists who were dedicated to the comprehensive management of all anticoagulants utilized during the inpatient setting. When PDAS was not available, DTIs were managed by the other pharmacists, assuring a 24/7 coverage by a pharmacist.[15]

Patients were excluded if they had a previous heparin allergy or a history of HIT, if they were not treated with an alternative anticoagulant, if treatment was stopped before ELISA results were available, or if treatment duration was not available. Additionally, we excluded cases occurring before 2007, which is when the specialized pharmacy service (the PDAS) started managing anticoagulation in all patients with suspected HIT. This time frame was chosen because the PDAS was shown in a previous study to improve dosing efficiency and decrease risk of major bleeding.[15] Therefore, this analysis was limited to the time frame that PDAS was available in order to minimize the influence the service may have on length of stay and bleeding risk.

Table 1. Direct Medical Costs Associated With Suspected HIT.

Laboratory testing	Bleeding/blood bank
ELISA	RBC
SRA	Platelets
Platelets with or without CBC	Cryoprecipitate
PT/INR	FFP
aPTT	Blood typing, compatibility, and cross-matching
Diagnostic procedure	Surgical intervention
Duplex ultrasound (extremities)	IVC filter placement
CT scan (head, chest, abdomen, pelvis, and extremities)	Amputation (extremities)
MRI (brain)	Embolectomy/thrombectomy (extremities)
V/Q scan	Bypass graft (extremities)
Angiography (extremities)	
Direct thrombin inhibitor	
Argatroban	
Lepirudin	

Abbreviations: SrCr, serum creatinine; CT, computed tomography; MRI, magnetic resonance imaging; V/Q, ventilation/perfusion; INR, international normalized ratio; CBC, complete blood count; IVC, inferior vena cava; RBC, red blood cell; FFP, fresh frozen plasma; PT, prothrombin time; aPTT, activated partial thromboplastin time; SRA, serotonin release assay; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia.

Patients with the SRA ordered as part of their diagnostic evaluation (SRA) were compared to those who did not (NSRA). ELISA (LIFECODES® PF4 Enhanced® assay; Gen-Probe Incorporated, Waukesha, Wisconsin) was considered positive irrespective of OD values since those values were not initially reported and thus not available for all patients. However, whenever OD was available, these values were reported and classified as weak positive (OD of 0.4-1) or strong positive (OD > 1). SRA was ordered by the primary team or as recommended by the pharmacist or the hematology/oncology service. SRA was not performed on site but rather sent out to multiple outside laboratories. A positive assay was defined as 20% or greater serotonin release.

The primary clinical end point, a composite of in-hospital mortality and major bleeding, defined by the International Society on Thrombosis and Haemostasis criteria, was compared between the SRA and the NSRA groups.[16] Secondary clinical end points included total rate of thrombosis as well as new thrombosis associated with HIT suspicion. Additionally, cost analysis according to SRA usage was performed, which included both the direct medical costs related to HIT management and the total cost of hospitalization. Direct medical costs included those associated with the diagnosis of HIT, the use of alternative anticoagulants, and the management of HIT-related complications (Table 1).

Hospital charges were obtained from the Henry Ford Health System Corporate Data Store and converted to costs. For each charge component, we used the specific cost to charge ratio that corresponds to its revenue center as determined by the hospital policy. All costs were reported in 2011 US dollar values and a 3%/year inflation rate was applied.

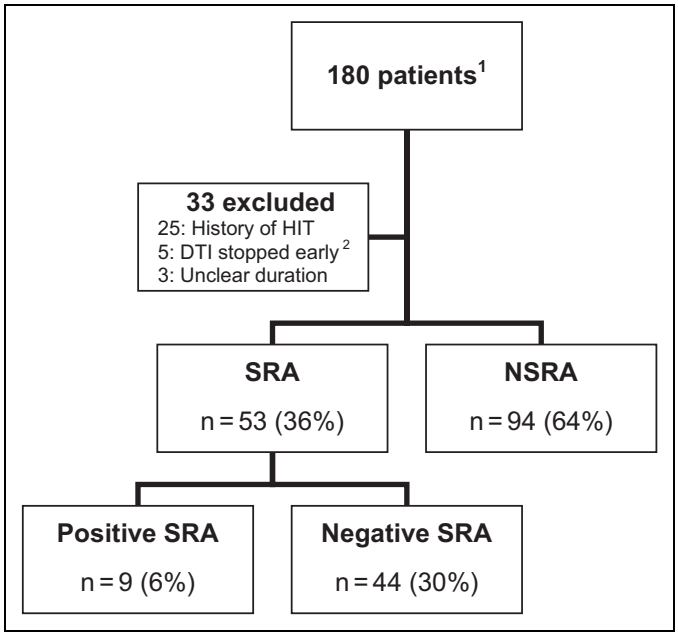

Figure 1. Patient distribution. [1]A total of 180 patients met the initial inclusion criteria: positive enzyme-linked immunosorbent assay (ELISA) and treatment with a direct thrombin inhibitor (DTI). [2]DTI stopped prior to ELISA results.

A separate subgroup cost analysis was performed to evaluate the cost of false-positive HIT, defined as an initial positive ELISA, followed by a negative SRA. Additionally, since the SRA was not available onsite, and was sent to an outside laboratory, we examined the average time delay for results to be reported. Finally, to account for earlier availability of those results, patients in whom an SRA was ordered early (within 48 hours of HIT suspicion) were compared to those who had a late SRA (after 48 hours of HIT suspicion).

Data Analysis

Data were reported with the use of descriptive statistics and characterized by mean values with standard deviation or median values with interquartile range, as appropriate. Continuous data were compared between the 2 groups, with a Student *t* test or Mann-Whitney *U* test, depending on the data distribution. For categorical data, chi-square or the Fisher exact test was used, as appropriate. A *P* value less than .05 was considered statistically significant.

Results

Patient Characteristics

A total of 180 patients with a positive ELISA and treated with a DTI were initially screened of which 147 met the inclusion criteria (Figure 1). SRA was performed in 53 patients of which only 17% were positive. Additionally, ODs were reported in 32 (21.8%) patients. In the SRA group, 0 of the 8 SRAs were positive in patients with OD of 0.4 to 1 (weak positive) and 3 of the 9 were positive in patients with OD > 1 (strong positive).

Patients in the NSRA group were older, more likely to be African American, and more likely to be female (Table 2). Additionally, higher thrombosis rates were seen in patients in the NSRA cohort. No differences were seen in the remaining clinical baseline characteristics, including the initial diagnosis at admission. Both groups had similar length of stay prior to HIT, with a median (range) of 8 days (3-13) of which 4 days (0-9) were spent in an intensive care unit.

Clinical Outcomes

The rate of primary composite end point was similar whether an SRA was ordered or not (32.1% vs 33%, $P = .911$). No difference in mortality was noted (24.5% vs 26.6%, $P = .783$). The median length of stay was 22 days in both the groups (Table 3). When looking at the number of days spent after HIT was initially suspected, patients in the SRA group stayed longer in the hospital, with a median of 16 days, compared to 12 days in patients in whom no SRA was performed ($P = .043$).

Cost of Illness

The total cost of hospital stay, per patient, was similar between the SRA and the NSRA groups (US $84781.1 vs US $78534.4, respectively, $P = .409$; Table 4). Additionally, there was no difference in the total cost after initial suspicion of HIT, defined by a positive ELISA and DTI started (US $52202.6 vs US $39285.2, $P = .199$), nor in the direct medical costs associated with HIT management (US $7473.5 vs US $8402.4, $P = .733$; Table 4).

The use of DTIs accounted for the majority of the direct medical costs, with an average duration of treatment of 8 days in the SRA group and 7.5 days in the NSRA group ($P = .359$; Table 3).

The total cost of hospital stay associated with false-positive ELISA was US $92896.4 per patient (53110.9-147962.1) of which US $47801.1 (27952.3-89667.7) occurred after the initial suspicion of HIT. Total duration of DTI treatment was 8 days (4.5-11.5) and the direct medical cost associated with false-positive HIT was US $7624.3 (3865.7-15403.8).

Subgroup Analysis Based on the Timing of the SRA

Since the SRA is sent to an outside laboratory at our institution, the average time for the results to be reported was approximately 9 days. Subsequently, only 40.9% of the SRA results were reported during inpatient HIT management. The remaining samples were reported after the completion of evidence-based therapy, as directed by the hospital guidelines, and the discontinuation of the DTIs. When available, a negative SRA led to the discontinuation of the DTIs in most of the patients and subsequently 33.3% of the patients were discharged within 48 hours. Performing the SRA early (within 48 hours) was associated with a shorter total length of stay (20 vs 27 days, $P = .029$), and a shorter hospitalization after HIT was suspected (12.5 vs 20, $P = .04$), although no difference in the cost of treatment was observed (Table 5). Additionally, the primary clinical outcome

Table 2. Baseline Characteristics.

	Total N = 147	NSRA N = 94	SRA N = 53	*P* value
Age, mean ± SD	61.2 ± 15.1	63.8 (±14.9)	56.5 (±14.5)	.005
Female, n (%)	72 (49%)	53 (56.4%)	19 (35.8%)	.017
African American, n (%)	80 (54.4%)	57 (60.6%)	23 (43.4%)	.044
Caucasian, n (%)	51 (34.7%)	26 (27.7%)	25 (47.2%)	.017
Serum creatinine, mean ± SD	1.8 ± 1.7	1.9 ± 1.7	1.6 ± 1.7	.296
Dialysis, n (%)	14 (9.5%)	11 (11.7%)	3 (5.7%)	.231
Cardiothoracic surgery, n (%)	19 (12.9%)	13 (13.8%)	6 (11.3%)	.663
Active thrombosis prior to HIT, n(%)[a]	43 (29.3%)	35 (37.2%)	8 (15.1%)	.005
Total days before HIT, median (IQR)	8 (3-13)	8 (4-14)	7 (2-12.5)	.119
Total ICU days before HIT, median (IQR)	4 (0-9)	4 (0-9.5)	4 (0-7.5)	.599
Patient on warfarin prior to HIT, n (%)	20 (13.6%)	11 (11.7%)	9 (17%)	.370
Initial anticoagulant, n (%)				
Heparin	132 (89.6%)	83 (88.2%)	49 (92.2%)	.454
LMWH[b]	15 (10.4%)	11 (11.8%)	4 (7.8%)	
Initial heparin or LMWH dose, n (%)[c]				
Treatment[d]	85 (57.7%)	58 (61.3%)	27 (51%)	.239
Prophylaxis	62 (42.3%)	36 (38.7%)	26 (49%)	
Direct thrombin inhibitor, n (%)				
Argatroban	100 (68.3%)	66 (70.7%)	34 (64.1%)	.132
Lepirudin	47 (31.7%)	28 (29.3%)	19 (35.9%)	

Abbreviations: HIT, heparin-induced thrombocytopenia; LMWH, low-molecular-weight heparin; ICU, intensive care unit; IQR, interquartile range; NSRA, patients without the SRA; SRA, serotonin release assay; SD, standard deviation; UH, unfractionated heparin.
[a]Defined as thrombosis requiring anticoagulation that occurred before HIT was clinically suspected.
[b]Most of patients who were on LMWH also received UH at the same hospitalization.
[c]Dosing based on hospital protocol.
[d]Intravenous UH or subcutaneous LMWH higher than prophylaxis doses.

Table 3. Clinical Outcomes.

	Total N = 147	NSRA N = 94	SRA N = 53	*P* value
Mortality and/or major bleeding, n (%)	48 (32.7%)	31 (33%)	17 (32.1%)	.911
Mortality, n (%)	38 (25.9%)	25 (26.6%)	13 (24.5%)	.783
Major bleeding, n (%)	17 (11.6%)	9 (9.6%)	8 (15.1%)	.315
New thrombosis, n (%)[a]	44 (29.9%)	31 (33%)	13 (24.5%)	.283
Any thrombosis, n (%)[b]	76 (51.7%)	55 (58.5%)	21 (39.6%)	.028
Arterial thrombosis, n (%)	15 (10.2%)	10 (10.6%)	5 (9.4%)	.817
Duration of DTI treatment, median (IQR)	8 (4-13)	7.5 (4-13.2)	8 (5.5-13.5)	.359
Total hospital stay after HIT, median (IQR)	13 (8-21)	12 (7-20)	16 (10-22)	.043
Total hospital stay, median (IQR)	22 (15-33.5)	22 (14-34)	22 (16-36.5)	.486

Abbreviations: DTI, direct thrombin inhibitor; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; NSRA, patients without the SRA; SRA, serotonin release assay.
[a]Thrombosis occurring after the initiation of heparin and associated with clinical suspicion of HIT.
[b]Any thrombosis occurring before or after anticoagulation.

was numerically lower but statistically insignificant when SRA was performed earlier (20.8% vs 41.4%, $P = .111$).

Discussion

Although HIT is a relatively rare condition, treatment of suspected HIT is associated with a large economic burden. Despite advances in the treatment of this disorder, rates of complications and mortality are still high, leading to a poor prognosis once diagnosis is established.[17,18] A special importance lies in the rapid and accurate diagnosis of HIT. And although immunologic assays are most widely used, their relatively low specificity increases the risk of false positives and thus augments the overall cost of illness associated with suspected HIT. Several methods can be used to increase the accuracy of the diagnosis including the use of a confirmatory step with the ELISA or using the 4Ts clinical scoring system.[6-8] However, platelet activation assays remain the gold standard for HIT diagnosis.[2]

In our study, incorporation of the SRA into the diagnostic workup for suspected HIT did not improve clinical outcomes nor reduce associated monetary costs, which thus question the direct utility of this laboratory assay. Additionally, the low rate

Table 4. Median Costs (IQR) Based on Whether an SRA Was Part of Diagnostic Workup (USD).

	SRA	NSRA	*P* value
Before HIT was suspected	28897.8 (6146.4-50949.9)	27159.9 (10097.1-64079.2)	.616
After HIT was suspected[a]	52202.6 (27750.7-87557.6)	39285.2 (22750.2-80179.5)	.199
Laboratory	1493.3 (515.4-2746.4)	843.5 (370.2-2124.2)	.014
Imaging	1758.6 (754.8-3194.4)	1404.0 (471.6-3067.2)	.228
Pharmacy	10927.2 (5281.2-18427.7)	10502.9 (5154.8-17787.3)	.645
Blood bank	414.3 (22.3-2094.2)	186.9 (0-855.1)	.024
Operation room	606.9 (84.7-4256.7)	282.6 (0-1762.9)	.062
Hospital stay-other	33936.1 (16342.2-58971.6)	24623.8 (12170.1-46765.5)	.088
Direct HIT management	7473.5 (3865.7-14578.7)	8402.4 (3551.0-15376.1)	.733
Laboratory	137.0 (115-288.4)	153.4 (89.1-255.3)	.516
Imaging	80.3 (0-149.9)	75.3 (0-194.2)	.981
Direct thrombin inhibitors	5753.0 (2775.6-14241.5)	7458.7 (3022.4-14945.2)	.697
Blood bank	414.3 (22.3-2094.2)	186.9 (0-855.1)	.024
Surgical intervention	0 (0-0)	0 (0-0)	.227
Total cost	84781.1 (54767.9-140081.0)	78534.4 (43169-143640.9)	.409

Abbreviations: DTI, direct thrombin inhibitor; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; NSRA, patients without the SRA; SRA, serotonin release assay.
[a]Defined by a positive ELISA screening and treatment with a DTI.

Table 5. Median Costs (IQR) Based on When the SRA Was Performed.

	Late SRA (>48 h)	Early SRA (≤48 h)	*P* value
Before HIT was suspected	34385.2 (6331.3-49477.4)	21212.3 (6146.4-67625.1)	.820
After HIT was suspected[a]	60196.5 (28215.8-124070.5)	45341.3 (19136.9-73232.0)	.272
Laboratory	2083.9 (656.8-4767.9)	1367.9 (428.8-2071.9)	.096
Imaging	2567.6 (757.2-4035.8)	1249.4 (726.5-2805.6)	.179
Pharmacy	11218.6 (5444.8-19933.5)	10157.5 (4853.6-17131.4)	.681
Blood bank	721.9 (40.9-2616.5)	353.9 (0-1104.0)	.181
Operation room	507.4 (100.1-4985.5)	1216.5 (0-3452.9)	.747
Hospital stay-other	41099.5 (20091.8-72551.4)	29289.9 (12948.3-45847.7)	.219
Direct HIT management	8076.8 (4952.9-15769.4)	7264.4 (2610.1-14578.7)	.354
Laboratory	198.7 (119.1-348.1)	126.0 (113.3-170.7)	.078
Imaging	87.5 (14.9-187.9)	66.1 (0-136.1)	.276
Direct thrombin inhibitors	5784.1 (2775.6-14684.5)	5753.0 (2691.3-13928.8)	.842
Blood bank	721.9 (40.9-2616.5)	353.9 (0-1104)	.181
Surgical intervention	0 (0-0)	0 (0-0)	.839
Total cost	92208.5 (70308.1-221936.8)	73414.9 (31119.9-129853.1)	.185

Abbreviations: DTI, direct thrombin inhibitor; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; IQR, interquartile range; NSRA, patients without the SRA; SRA, serotonin release assay.
[a]Defined by a positive ELISA screening and treatment with a DTI.

of positive SRA results suggests that HIT is likely being overly suspected. This outlines the need to carefully interpret ELISA results in the context of the clinical presentation as an initial diagnostic approach while awaiting the confirmatory SRA results. The SRA would thus be of a potential benefit for those with extended duration of DTI treatment and as a valuable tool for subsequent use of heparin products.

Alternatively, the absence of cost reduction in our study might have been due, in part, to the significant delay in the reporting of the SRA results, which might have prevented clinicians from incorporating those results early into the clinical decision process. This is supported by the fact that ordering the SRA earlier during the diagnostic workup was associated with a reduction in hospital stay although no difference in costs was observed. Additionally, once available, negative results lead to the discontinuation of DTIs and hospital discharge in a significant proportion of patients. This suggests that clinicians are reacting to SRA results and that earlier ordering and reporting might have the potential to significantly reduce the cost and duration of hospitalization, specifically for patients with false-positive ELISA screening. The slow turnaround time of the SRA is in part due to the fact that it is not done in most hospitals but rather sent out to an outside laboratory as it is performed by skilled technicians in a radioisotope facility. As such, a cost–benefit analysis of performing this test within each hospital is needed.

Previous studies done in the United States have examined the cost of illness associated with this disorder. Those studies utilized

different definitions of HIT and had different study designs, leading to a different estimation of the cost of care.[9-14] The key difference between the previous literature and our study is that we examined the costs of all suspected HIT and separated the costs of true- and false-positive results as confirmed subsequently by an SRA. As such, this is the first study to examine the financial benefit of using functional tests in the diagnostic workup of patients with suspected HIT and the potential decrease in the cost of care associated with false-positive ELISA screening.

An interesting finding was the low rate of positive SRA tests for which several explanations can be proposed. First, as previously stated, this may reflect a low threshold to screen for HIT, especially in situations where high incidence of false-positive ELISA is known to occur, such as patients who have undergone a cardiothoracic surgery. On the other hand, this low rate may suggest a possible selection bias in which patients with a relatively low suspicion for HIT were ordered a confirmatory SRA whereas in those with higher level of suspicion (ie, thrombosis), a positive ELISA was considered sufficient to diagnose HIT. And this is likely why the NSRA group had a higher rate of thrombosis.

The results of this study must be viewed in the context of several limitations. First, the direct medical costs associated with HIT are underestimated as we did not account for the possible increase in length of stay, in which patients stayed in the hospital simply to be actively treated with an alternative anticoagulant. However, as no difference was seen in the length of stay, and as no evidence exists to suggest that the use of SRA may affect hospital stay, including this particular cost component would not have affected the results. Also, since this was a retrospective observational study, confounding factors cannot be completely ruled out. This was manifested in a longer hospital stay after HIT was suspected in the SRA group as well as some differences in the baseline characteristics. Finally, the generalizability of our results to other institutions will depend on the availability of SRA onsite and its turnaround time, the preferred alternative anticoagulant, the strategy used for waste minimization of these agents as well as the responsible provider for DTI management. At our institution, this latter is performed by a specialized pharmacy service, a strategy shown to improve dosing efficiency and decrease risk of major bleeding.[15]

In conclusion, the diagnosis and treatment of suspected HIT, including those associated with a false-positive ELISA screening, are associated with significant health care costs. The use of SRA was not associated with a benefit on clinical or financial outcomes. Further studies are needed to determine the benefit of having earlier access to the results by performing this assay within each health system.

Declaration of Conflicting Interests

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