Risk Factors in Hospitalized Patients for Heparin-Induced Thrombocytopenia by Real World Database: A New Role for Primary Hypercoagulable States

Jasmeet Kaur[a, d], Camelia Arsene[b], Sumeet Kumar Yadav[a], Olusola Ogundipe[c],
Ambreen Malik[a], Anupam Ashutosh Sule[a], Geetha Krishnamoorthy[a]

Abstract

Background: The aims of the study were to identify predictors of heparin-induced thrombocytopenia (HIT) in hospitalized adults, and to find additional factors associated with higher odds of HIT in primary hypercoagulable states.

Methods: A retrospective matched case-control study using discharge data from National Inpatient Sample database (2012 - 2014) was conducted. In primary outcome analysis, hospitalized patients with and without HIT were included as cases and controls, both matched for age and gender. In secondary outcome analysis, hospitalized patients with primary hypercoagulable states with and without HIT were included as cases and controls, both matched for age and gender. The statistical analyses were performed using Statistical Package for Social Sciences version 25.

Results: There are several predictors of HIT in hospitalized patients, such as obesity, malignancy, diabetes, renal failure, major surgery, congestive heart failure, and autoimmune diseases. In patients with primary hypercoagulable states, the presence of renal failure (odds ratio (OR) 2.955, 95% confidence interval (CI) 1.994 - 4.380), major surgery (OR 1.735, 95% CI 1.275 - 2.361), congestive heart failure (OR 4.497, 95% CI 2.466 - 8.202), or autoimmune diseases (OR 1.712, 95% CI 1.120 - 2.618) further increases the odds of HIT.

Conclusions: In hospitalized patients with primary hypercoagulable states, especially in association with renal failure, major surgery, con-gestive heart failure, or autoimmune diseases, unfractionated heparin should be used with caution.

Keywords: Heparin; Thrombocytopenia; Thrombophilia; Inpatients; Risk factors; Autoimmune diseases

[a]Department of Internal Medicine, St. Joseph Mercy Oakland Hospital, Pontiac, MI, USA
[b]Department of Medical Education, St. Joseph Mercy Oakland Hospital, Pontiac, MI, USA
[c]Department of Infectious Diseases, William Beaumont Hospital, Royal Oak, MI, USA
[d]Corresponding Author: Jasmeet Kaur, Department of Internal Medicine, St. Joseph Mercy Oakland Hospital, Pontiac, MI, USA.
Email: Jasmeet.Kaur001@stjoeshealth.org

Introduction

Heparin-induced thrombocytopenia (HIT) occurs when antibodies to platelet factor 4 (PF4) and heparin complexes bind to the FcγRIIA receptors on platelets and monocytes to begin a hypercoagulable state that may cause thrombosis [1]. Antibodies to PF4-heparin complexes are frequently detected in patients treated with unfractionated heparin. Thrombocytopenia occurs only in about 1% of those patients, and thrombosis develops in only 20% of those with thrombocytopenia [2, 3]. Factors that cause thrombocytopenia and thrombosis in a subset of patients with PF4-heparin antibodies are not well understood [1]. Orthopedic surgery, lower platelet count and higher titer of PF4-heparin antibodies have been shown to be concurrent factors that increase the risk of thrombosis in HIT [4]. Hemodialysis, autoimmune diseases, gout, heart failure, intravenous route of heparin and > 5 days of heparin use were found to increase the risk of HIT diagnosis in medical patients [5]. Obesity has been identified as a risk factor for HIT recently [6]. Patients with HIT were more likely to have autoimmune diseases, namely antiphospholipid antibody syndrome (APLA), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Hashimoto's thyroiditis and non-ischemic cardiomyopathy than patients without HIT in a hospital-based case-control study (55% vs. 10.8%, P < 0.001) [7].

Patients with primary hypercoagulable states have a higher risk of developing venous thromboembolism (VTE), and being exposed to heparin [8]. There is a paucity of data on the relationship between primary hypercoagulable states and HIT.

In our study, we first identified factors that increase the odds of HIT in hospitalized patients, and then the association between primary hypercoagulable states (International Classification of Diseases, Ninth Revision (ICD-9: 289.81) and HIT (ICD-9: 289.84)).

Materials and Methods

Patient selection

The study was a matched case-control study that was conducted using discharge data from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality [9]. This study was conducted in compliance with all the applicable institutional ethical guidelines for the care, welfare and use of animals. The NIS database provides de-identified information about the patients' demographics and hospital-based information. Besides, it provides information about the days to readmission and readmission status. Since a publicly available database was used, the study was considered exempt from obtaining permission from the institutional review board.

The primary objective of the study was to identify predictors of HIT in hospitalized patients. Inclusion criteria included adults (> 18 years old) admitted for HIT (International Classification of Diseases, Ninth Revision (ICD-9: 289.84) to hospitals that shared their data with HCUP. For each year, cases and controls were matched by age and gender. The coding accuracy of HIT was well developed in a national database study [10].

The secondary objective was to identify factors that increase the odds of HIT in patients with primary hypercoagulable states. For this analysis, hospitalized patients with a primary diagnosis of hypercoagulable states (ICD-9: 289.81) and HIT were included as cases while hospitalized patients with a diagnosis of primary hypercoagulable states but no HIT were included as controls. Cases and controls were matched by age and gender.

Definition of terms

Primary hypercoagulable states (ICD-9: 289.81) include APLA (including pregnancy-related and postpartum APLA), homozygous and heterozygous forms of inherited protein C and S and antithrombin deficiencies, prothrombin G20210A mutation, and factor V Leiden, and thrombophilias due to acquired protein C, S and antithrombin deficiencies. Per HCUP comorbidity definition, obesity includes overweight, obesity and morbid obesity; metastatic cancer includes ICD-9-CM codes: 196.0-199.1 (Supplementary Material 1, www.thejh.org); renal failure includes benign, malignant and unspecified hypertensive chronic kidney disease (CKD) stage V or end-stage renal disease (ESRD) with and without heart failure, CKD stages I-V, unspecified renal failure, kidney transplant, renal dialysis encounter and fitting and adjustment of peritoneal dialysis catheter; weight loss includes marasmus, Kwashiorkor and all degrees of protein-calorie malnutrition and unspecified malnutrition; major surgeries include procedure class 4, which are major therapeutic operating room procedures as per diagnostic related group (DRG) grouper and done for therapeutic reasons; congestive heart failure (CHF) includes rheumatic heart failure, benign, malignant and unspecified hypertensive heart disease with heart failure, benign, malignant and unspecified hypertensive heart and CKD with heart failure and CKD I-IV, left heart failure, systolic, diastolic, and combined systolic and diastolic and unspecified heart failures; autoimmune diseases include SLE and RA. Detailed definitions are available in HCUP comorbidity software [11].

Statistical analyses

We performed descriptive statistics on the variables of interest defined below. For categorical variables, Chi-square or Fisher's exact tests were performed. Differences between the groups for continuous variables were measured by the Student's t-test. P values of < 0.05 were considered statistically significant.

Comorbid conditions previously shown to be associated with increased risk of VTE or HIT such as obesity, solid tumor without metastases, metastatic cancer, uncomplicated diabetes, diabetes with chronic complications, renal failure, weight loss, primary hypercoagulable states, major surgery, CHF, and autoimmune diseases (SLE, RA) were included in univariate analyses, and if statistically significant, in multivariate regression analyses [8, 12-15].

All analyses were performed using Statistical Package for Social Sciences (SPSS) version 25.

Results

Analyses on HIT patient groups

From a total of 21,488,293 inpatient admissions based on discharge level data in NIS database during the study years 2012 - 2014, there were 12,406 cases of HIT across the 3 years that were compared with an equivalent number of patients without HIT and matched by age and gender. The overall incidence of identified HIT was 57.7 per 100,000 cases (hospitalized patients) in our study. In univariate analyses, the hospitalized patients with HIT and hospitalized patients without HIT were different in regard to certain comorbid conditions, as presented in Table 1. Multivariate analyses are presented in Table 2. HIT was present in 36.5% of patients with major surgery, 33.5% patients with renal failure and 25.8% patients with uncomplicated diabetes. HIT was also present in 3.4% of patients with primary hypercoagulable states and 3.9% of patients with autoimmune diseases.

In univariate analyses, we found that HIT was more likely to occur in primary hypercoagulable states (3.4% versus 0.3%, P < 0.0005). Patients with HIT had higher inpatient mortality when compared to patients without HIT (9.6% versus 2.6%, P < 0.0005). In multivariate analysis, the odds ratio (OR) for HIT in primary hypercoagulable states was 11.338 (95% confidence interval (CI) 8.104 - 15.863), as presented in Table 2.

Factors associated with HIT among patients with hypercoagulable states

There were 80,973 cases across the 3 years (2012 - 2014) with hypercoagulable states based on discharge level data in NIS

Table 1. Univariate Analyses for Patients Without HIT Compared to Patients With HIT

Variable	Patients without HIT (N = 12,406)	Patients with HIT (N = 12,406)	P value
Age	64.8 ± 15.5	64.8 ± 15.5	1.000
Gender - female	6,091 (49.1%)	6,091 (49.1%)	1.000
Obesity	1,590 (12.8%)	2,188 (17.6%)	< 0.0005*
Solid tumor without metastases	313 (2.5%)	438 (3.5%)	< 0.0005*
Metastatic cancer	309 (2.5%)	515 (4.2%)	< 0.0005*
Lymphoma	141 (1.1%)	130 (1.0%)	0.502
Uncomplicated diabetes	2,774 (22.4%)	3,205 (25.8%)	< 0.0005*
Diabetes with chronic complications	733 (5.9%)	1,280 (10.3%)	< 0.0005*
Drug abuse	523 (4.2%)	439 (3.5%)	0.006*
Renal failure	1,875 (15.1%)	4,152 (33.5%)	< 0.0005*
AIDS	35 (0.3%)	35 (0.3%)	1.000
Primary hypercoagulable states	39 (0.3%)	416 (3.4%)	< 0.0005*
Major surgery	2,992 (24.1%)	4,533 (36.5%)	< 0.0005*
Congestive heart failure	1,304 (10.5%)	2,560 (20.6%)	< 0.0005*
Autoimmune disease	256 (2.1%)	489 (3.9%)	< 0.0005*

*P < 0.05 statistically significant. HIT: heparin-induced thrombocytopenia; AIDS: acquired immunodeficiency syndrome.

database. For each year, cases and controls were matched by age and gender. The final sample size included a total of 416 cases in each group.

In secondary analyses, we included risk factors that have previously been reported to increase the risk of HIT to find out if they further increase the risk of HIT in patients with primary hypercoagulable states (Tables 3 and 4). Patients with HIT and hypecoagulable states were more likely to die when compared to patients without HIT and hypercoagulable states (5.8% versus 2.9%) but the result was not statistically significant (P < 0.059).

In multivariate logistic regression analysis, HIT occurred more frequently in patients with primary hypercoagulable states and also renal failure (OR 2.955, 95% CI 1.994 - 4.380),

major surgery (OR 1.735, 95% CI 1.275 - 2.361), CHF (OR 4.497, 95% CI 2.466 - 8.202), or autoimmune diseases (OR 1.712, 95% CI 1.120 - 2.618).

Discussion

We started by identifying several factors associated with a higher likelihood of developing HIT in hospitalized patients. While Warkentin et al found that female orthopedic and cardiac surgical patients treated with unfractionated heparin have an increased risk of HIT, other studies did not identify female gender as a risk factor [4, 5, 16]. In our study, we matched cases and controls for age and gender and did not study if either of

Table 2. Multivariate Logistic Regression Analysis for Patients With HIT

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	P value
Obesity	1.377	1.276	1.486	< 0.0005*
Tumor	1.680	1.436	1.966	< 0.0005*
Metastatic cancer	1.900	1.628	2.217	< 0.0005*
Uncomplicated diabetes	1.183	1.109	1.263	< 0.0005*
Diabetes with chronic complications	1.326	1.192	1.474	< 0.0005*
Drug abuse	1.150	1.000	1.323	0.05*
Renal failure	2.670	2.497	2.856	< 0.0005*
Primary hypercoagulable state	11.338	8.104	15.863	< 0.0005*
Major surgery	2.100	1.978	2.229	< 0.0005*
Congestive heart failure	1.985	1.836	2.145	< 0.0005*
Autoimmune disease	1.753	1.484	2.072	< 0.0005*

*P < 0.05 statistically significant. HIT: heparin-induced thrombocytopenia; CI: confidence interval.

Table 3. Univariate Analyses for Patients With Primary Hypercoagulable States and No HIT Compared to Patients With Primary Hypercoagulable States and HIT

Variable	Patients with primary hypercoagulable states and no HIT (N = 416)	Patients with primary hypercoagulable states and HIT (N = 416)	P value
Age	53.4 ± 16.6	53.4 ± 16.6	1.000
Gender - female	248 (59.6%)	248 (59.6%)	1.000
Obesity	66 (15.9%)	75 (18.0%)	0.460
Solid tumor without metastases	4 (1.0%)	12 (2.9%)	0.074
Metastatic cancer	10 (2.4%)	17 (4.1%)	0.240
Lymphoma	6 (1.4%)	3 (0.7%)	0.505
Uncomplicated diabetes	70 (16.8%)	89 (21.4%)	0.112
Diabetes with chronic complications	13 (3.1%)	28 (6.7%)	0.024*
Drug abuse	21 (5.0%)	19 (4.6%)	0.872
Renal failure	45 (10.8%)	123 (29.6%)	< 0.0005*
AIDS	0.0 (0.0%)	0.0 (0.0%)	N/A
Major surgery	119 (28.6%)	161 (38.7%)	0.003*
Congestive heart failure	15 (3.6%)	64 (15.4%)	< 0.0005*
Autoimmune disease (SLE, RA)	46 (11.1%)	78 (18.8%)	0.002*

*P < 0.05 statistically significant. HIT: heparin-induced thrombocytopenia; AIDS: acquired immunodeficiency syndrome; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis.

these factors increased the risk of HIT. The overall incidence of HIT was 57.7 per 100,000 cases (0.057%). A similar study by Dhakal et al reported 0.065% (0.001% SE) incidence of HIT that is 1 in every 1,500 hospitalized patients [10].

Obesity significantly increased the likelihood of HIT (OR 1.377, 95% CI 1.276 - 1.486) in our analysis. Bloom et al reported an increased risk of developing HIT in obese patients (body mass index (BMI) > 30 kg/m^2) in surgical and cardiac intensive care units, and Marler et al in medical intensive care and general medical ward patients [6, 17]. The NIS database studies have shown that the incidence of HIT is high among patients undergoing cardiac surgeries and interventions such as aortic valve replacement and is associated with high risk of in-hospital mortality and post-operative complications [18, 19]. Subsequently, patient "thickness", timing of thrombocytopenia and other causes of thrombocytopenia, a 3T score has been found to be associated with a higher predictive accuracy of HIT in surgical and cardiac intensive care units [20]. Obesity has been shown to be associated with a higher prevalence or worse outcomes in several immune-mediated disorders such as RA and SLE [21, 22]. Obesity

has been found to contribute to both a hypercoagulable state and platelet hyperaggregability, and has been shown to increase the risk of VTE [12, 23, 24]. Furthermore, platelets from obese individuals have been shown to exhibit increased aggregation in response to adenosine diphosphate due to increased leptin levels [25].

Metastatic cancer was associated with higher odds of HIT. Prior small studies reported that adenocarcinoma, and non-hematological malignancy increased the risk of HIT [26, 27]. There are limited data on HIT in cancer patients, and our results suggest the need for further research in this area.

Diabetes increased the likelihood of HIT in our analysis. Prechel et al found that although the prevalence of positive PF4-heparin antibody results in hospitalized patients with or without diabetes was not different compared to healthy volunteers, the titer was significantly higher in hospitalized diabetic patients with infection and those not on medications [28]. They also found a significantly lower PF4-heparin antibody titer in well-controlled ambulatory diabetics [28]. In our study, the odds of HIT in uncomplicated diabetes were further increased by the presence of chronic complications supporting Prechel's

Table 4. Multivariate Logistic Regression Analysis for Patients With HIT and Primary Hypercoagulable States

Variable	Odds ratio	Lower 95% CI	Upper 95% CI	P value
Diabetes with chronic complications	1.561	0.753	3.235	0.231
Renal failure	2.955	1.994	4.380	< 0.0005*
Major surgery	1.735	1.275	2.361	< 0.0005*
Congestive heart failure	4.497	2.466	8.202	< 0.0005*
Autoimmune disease	1.712	1.120	2.618	0.013*

*P < 0.05 statistically significant. HIT: heparin-induced thrombocytopenia; CI: confidence interval.

hypothesis that comorbidities associated with diabetes (macrovascular disease, obesity, hypertension and hyperlipidemia) cause vascular inflammation. The inflammation increases PF4 level leading to higher PF4-heparin antibody generation, and medications to treat these comorbidities may annul the immunogenic environments [28].

Patients with renal failure had increased association with HIT as reported previously [5]. PF4-heparin antibodies have been detected in up to 12% of patients on dialysis, but only a minority develop HIT [29]. Although the factors that determine who will progress to HIT may not be understood, multiple studies have demonstrated an association of the PF4-heparin antibody titer with mortality in hemodialysis patients [30-32]. Extreme obesity and advanced renal failure are frequently reasons for using unfractionated heparin in hospitalized patients, and this poses an increased risk for HIT in these patient groups.

HIT has been reported to be more frequent in patients with acquired hypercoagulable states such as essential thrombocytosis (ET) with V617F mutation [33]. IgG PF4-heparin antibodies occur endogenously in polycythemia rubra vera (PV) even in the absence of concurrent heparin exposure, increasing the thrombosis risk [34]. Since HIT is an acquired thrombophilia, that has been reported to be increased in other prothrombotic states such as ET, PV, malignancies, and surgery, we analyzed the relationship between primary hypercoagulable states and HIT.

Our multivariate analysis found that primary hypercoagulable states were present in 3.4% of patients and were significantly associated with HIT (OR 11.338, 95% CI 8.104 - 15.863). This may be due to the fact that patients with primary hypercoagulable states had more frequent thrombotic complications and required treatment with heparin or low molecular weight heparin. Case reports of HIT with thrombosis in patients with primary hypercoagulable states including factor V Leiden, protein S deficiency and antithrombin deficiency have been published [35-37]. Lindhoff-Last et al did not detect a difference between patients with HIT and controls in factor V Leiden, prothrombin G-20210 mutation, antithrombin, proteins C, S, and factor XII deficiencies, and antiphospholipid antibodies [38]. Factor VIII levels were found to be higher in HIT patients [38].

Factors such as obesity, metastatic and non-metastatic tumors, lymphoma, diabetes with and without complications, or weight loss which increase the odds of HIT in the general population as seen in our first analysis, do not increase the risk of HIT any further in the presence of primary hypercoagulable states. Additional factors that increase the odds of HIT in patients with primary hypercoagulable states include renal failure, major surgery, CHF, or autoimmune diseases. An NIS database-based study by Pathak et al reported cardiovascular and orthopedic surgeries were significantly associated with the occurrence of HIT [39].

Patients with CKD have been found to have higher final clot strength and decreased breakdown of clot, due to supranormal fibrinogen levels [40]. It is possible that the increased thrombin generation associated with primary hypercoagulable states and the higher fibrinogen level found in renal failure may mediate platelet aggregation due to fibrinogen as well as by thrombin (novel glycoprotein 1b-mediated mechanism)

[41].

Kato et al found that patients with autoimmune diseases had a relative risk of 3.47 (95% CI 1.93 - 6. 26, P < 0.0001) for development of HIT [5]. Klinkhammer et al also found that patients with HIT were more likely to have autoimmune disease as a comorbidity (55.9% vs. 10.8%, P < 0.001) [7]. Mechanisms proposed to be common to HIT and autoimmune disorders include the formation of PF4-heparin "neoantigen" (similar to citrullinated proteins in RA), the formation of IgG antibody to the PF4-heparin complex (similar to post-vaccination Arthus reaction), and the triggering of release of PF4 antigen by binding of anti-PF4 antibody (similar to damage-mediated release of myelin basic protein in multiple sclerosis) [7]. Although association of APLA and HIT with extensive thrombosis was reported in two cases, a large proportion of patients with APLA and/or SLE were found to have false positive PF4-heparin antibody results in a study by Pauzner et al [42-44]. HIT may have been overdiagnosed in patients with autoimmune diseases, particularly APLA, leading to the association we detected between autoimmune diseases and HIT in both patients with and without primary hypercoagulable states. Major surgery, particularly orthopedic surgery and heart failure have been reported to be associated with HIT, and this association continues to be significant in the presence of primary hypercoagulable states as well [4, 5].

There are some limitations to our analysis. Our retrospective study used administrative diagnosis codes from a national database. Our main methodological limitation is that it is a secondary data analysis by performing a matched case-control study, using data already collected for other purposes. This limits the ability to match or adjust for clinical parameters like 4T scores or amount, frequency, nature or route of heparin administration, because individual clinical characteristics or treatment data are not available in NIS. Even though the heparin administration factors were not matched/adjusted, the study results are valid because the probability of having received heparin for a patient suffering from the comorbidities we studied would be similar given that controls were randomly picked. An exception to the above argument is that patients with primary hypercoagulable states were more likely to have thromboembolism and were more likely to be exposed to heparin, accounting for the higher proportion of HIT in this group. In the second part of the study, both cases and controls had primary hypercoagulable states, with similar probability of receiving heparin.

Conclusions

Caution should be used when unfractionated heparin is being considered in patients with obesity, solid organ metastatic and non-metastatic tumors, diabetes with and without complications, renal failure, major surgery, CHF, or autoimmune diseases as these factors were found to increase the odds of HIT.

In patients with primary hypercoagulable states, the presence of renal failure, major surgery, CHF, or autoimmune diseases was associated with the occurrence of HIT.

Prospective studies for the use of heparin alternatives and

more effective treatments are needed in patients with high risk factors for HIT.

Supplementary Material

Suppl 1. ICD-9-CM codes.

Conflict of Interest

The authors have no conflict of interest to declare.

Informed Consent

No applicable as this was a retrospective study.

Author Contributions

GK, JK, OO and AS were involved in the conception and initial design of the study. GK, AS, CA, SKY, JK, OO, and AM were involved in the initial literature review and data interpretation and wrote the initial draft of the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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