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Association of medical comorbidities in obese subjects diagnosed with heparin-induced thrombocytopenia

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Abstract

Objectives: Heparin-induced thrombocytopenia can occur in obese subjects. The medical comorbidities associated with obesity may contribute to the pathogenesis of this disease. It is unknown, however, which specific medical comorbidities and if higher odds of thrombosis are present in obese heparin-induced thrombocytopenia patients. We sought to determine whether obese heparin-induced thrombocytopenia subjects had higher odds of both comorbidities and thrombosis, hypothesizing that this patient population would have higher odds of both these conditions.

Methods: This was a multi-center retrospective study utilizing TriNetX©, an electronic health record database, in subjects aged 18–99 years diagnosed with heparin-induced thrombocytopenia. The cohort was divided into two groups (1) non-obese (body mass index $< 30\,kg/m^2$) and (2) obese (body mass index $\geq 30\,kg/m^2$). We evaluated patient characteristics, diagnostic, laboratory, medication, and procedure codes.

Results: A total of 1583 subjects (696 (44.0%) non-obese and 887 (56.0%) obese) were included. Obese subjects had higher odds of diabetes with complications (OR = 1.73, 95% CI = 1.35–2.22, $p < 0.001$) and without complications (OR = 1.81, 95% CI = 1.47–2.22, $p < 0.001$). This association was still present after correcting for demographic and clinical factors. There were no increased odds of thrombosis observed in the obesity group.

Conclusions: Our study found that obese heparin-induced thrombocytopenia subjects had higher odds of having a diabetes mellitus comorbidity, but did not have higher odds of thrombosis. Given obesity is considered a hypercoagulable state, further study may be needed to understand why obese subjects diagnosed with heparin-induced thrombocytopenia do not have higher rates of thrombosis.

Keywords

Obesity, heparin, comorbidity, thrombosis

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Introduction

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated complication of heparin therapy that can result in a life-threatening hypercoagulable state.[1] It is characterized by the generation of autoantibodies against the complex formed when heparin binds to endogenous platelet factor 4 (PL4).[1] This type 2 hypersensitivity reaction causes platelet activation and destruction. The resultant thrombosis can lead to skin necrosis, limb loss, and organ infarction.[1] HIT occurs in an estimated 0.2%–3% of patients with exposure to heparin,[2–4] but significant morbidity and mortality can occur if it progresses unrecognized or if thrombosis occurs.[5,6] Prompt

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recognition and intervention, therefore, are necessary to reduce poor outcomes.

Unfortunately, no test reliably diagnoses HIT in a timely manner. The common "4Ts" scoring system can help to determine the pretest probability of HIT and has a high negative predictive value.[7,8] Thus, it can rule out this disease. Higher 4T scores, however, have a lower positive predictive value.[7,8] HIT immunoassays can be used to detect anti-PF4 antibodies, but indeterminant results and variable diagnostic accuracy limit their utility.[9] The gold standard for diagnosis is the functional assay, which measures the ability of the PF4-heparin antibodies to cause platelet activation. However, despite their high sensitivity and specificity, functional assays may only be available within laboratories outside the institution and can take days to result.[10,11] With no singular test to both promptly and accurately diagnose HIT, management relies heavily on the assessment of clinical findings, as clinicians must initiate treatment before immunoassay and functional assay results provide a definitive diagnosis. It is therefore important to identify those patients receiving heparin therapy at increased risk of developing HIT to aid in prompt diagnosis and treatment.

Obesity is considered a hypercoagulable and chronic inflammatory state that is associated with an increased risk of venous thromboembolism, arterial thrombosis, and cardiovascular disease.[12–14] More recently, obesity has also been identified as a risk factor for the development of HIT.[8,15–17] There is still much to learn about the association between obesity and HIT. For example, based on current literature, it is unclear whether obesity independently increases the risk of HIT, or whether the two are linked because obese patients are more likely to experience complications that all independently increase the risk of HIT (such as higher rates of hospitalization,[18,19] prolonged length of stay,[20,21] diabetes and other medical comorbidities associated with the metabolic syndrome,[22] and renal disease necessitating use of unfractionated rather than low molecular weight heparin[23]).

An understanding of the impact of obesity and its associated comorbidities in HIT subjects and its outcomes may enhance our diagnostic approach to this disease process. Using a multicenter electronic health record (EHR) database, we sought to determine whether any identified comorbidities had higher odds of being present in obese subjects with HIT, as well as whether thrombosis was positively associated in obese subjects with HIT. We hypothesized that in subjects with a HIT diagnosis, there would be a higher proportion of obese subjects with hypercoagulable associated comorbidities (particularly myocardial infarction and diabetes mellitus) and thrombosis diagnoses in obese subjects.

Methods

Study design

This is a retrospective observational cohort study utilizing the TriNetX® EHR database of subjects with HIT.

Data source

TriNetX is a global federated research network that is primarily based in the United States. Using a proprietary algorithm, it collects aggregated EHR data elements (including diagnoses, medications, procedures, and laboratory values) of approximately 68 million patients in 56 large healthcare organizations (HCOs). These data elements are made available within a user-friendly browser-based software in real-time after de-identification. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA), a United States federal law that ensures healthcare information privacy and security, and any additional data privacy regulations applicable to the contributing HCO. TriNetX is certified to the ISO 27001:2013 standard and maintains an Information Security Management System (ISMS). This ensures that HIPAA Security Rule requirements are met and the protection of the healthcare data it is provided access to. The data sets generated by the TriNetX Platform are patient level and contain only de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The data de-identification process is attested to through a strict determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule.

Ethical considerations

Because no protected health information is provided, the Penn State Health Institutional Review Board (IRB) predetermined this study to be non-human research (STUDY 00020794).

Data collection

The data used in this study were collected on 30 August 2022 from the TriNetX Research Network. After the dataset was received, we analyzed the following EHR data: age, sex, race, ethnicity, diagnostic codes, medication codes, procedure codes, laboratory codes, body mass index (BMI) codes, and all-cause 1-year mortality.

Inclusion and exclusion criteria

We included subjects who were (1) aged 18–99 years, (2) had a diagnostic code associated with HIT (International Classification Code of Diseases, 10th edition (ICD-10), D75.82) for the first time in their EHR database history, (3) had received argatroban 30 days before and after diagnosis, and (4) had a BMI value present 30 days before and after diagnosis. In addition, to increase the likelihood that the date and time of the HIT diagnostic code was the first time the patient was diagnosed, we only included patients who (5) had a serotonin release assay level obtained, and the result, when present, was above 20%. We excluded patients who did not have all five of these criteria.

Argatroban was the only non-heparin anticoagulant utilized to identify this patient cohort, primarily because of its wider availability.[24] We also wanted to ensure that the patient was hospitalized for this condition (i.e., argatroban is administered intravenously), thereby allowing the examination of diagnostic codes (particularly those associated with imaging) during the time period when HIT was diagnosed.

Cohort designation

After identifying subjects with a recorded BMI, the cohort was divided into two groups (non-obese (BMI $< 30\,kg/m^2$) and obese (BMI $> 30\,kg/m^2$)).

Variables

The primary outcomes of interest were the presence of diagnostic codes associated with HIT, medical comorbidities, and thrombosis. Using International Classification of Diseases, 9th (ICD-9) and ICD-10 diagnostic codes prior to the first date of the HIT diagnosis, we identified Charlson comorbidities using the "Comorbidity" package in R.[25]

Secondary outcomes included patient characteristics (age, sex, race, ethnicity), laboratory values (serotonin release assay), vital signs (BMI), medications (argatroban), procedures (central venous lines), and all-cause mortality (the frequency of deaths within 365 days of HIT diagnosis). Please see Supplemental Table 1 for diagnostic, medication, and procedural code definitions that were analyzed in this present study.

The data provided were de-identified; thus no date of birth was provided, and thus, ages are approximate. For example, if a subject born in 2000 was reported to have a HIT diagnosis on 1 January 2018, the subject was determined to be 18 years of age. Due to database limitations, the dates but not the times were provided for laboratory results. Thus, for the BMI and serotonin release assay, we recorded the maximum value 30 days before and after HIT diagnosis. Not all laboratory tests, especially the serotonin release assay, are widely available. Thus, we recorded only the results accessible through the TriNetX database as we were unable to access any laboratory results that were potentially sent outside the subject's institution.

Statistical analysis

Two-way contingency tables were created to summarize counts for pairwise combinations of variables of interest. The oddsratio() function in the epitools R package was then applied to compute odds ratios and associated 95% confidence intervals using the "wald" option.[26] In addition, Fisher's exact test p-values were computed followed by a Bonferroni adjustment based on the total number of variables considered. Multivariable logistic regression models were fit to assess the impact of obesity on binary outcomes of interest while controlling for select covariates. Confidence intervals for parameter estimates in the logistic regression models were calculated with the confint2() function in the glmtoolbox R package using the "wald" option.[27] The Wilcoxon rank sum test was applied to perform two-sample tests involving quantitative variables. All analyses were performed with R 4.2.0.[28]

Results

Overview

A total of 1583 subjects (696 (44.0%) non-obese and 887 (56.0%) with obesity) were included. Non-obese subjects and obese subjects had a mean BMI of 24.97 ± 3.48 and $36.79 \pm 5.45\,kg/m^2$, respectively. There was no difference in age, sex, race, ethnicity, mortality, and central venous access. Subject demographics are summarized in Table 1.

Pre-existing Charlson comorbidities

Of the subjects with pre-existing Charlson medical comorbidities, higher odds of diabetes with (OR = 1.73, 95% CI = 1.35–2.22, $p < 0.001$) and without complications (OR = 1.81, 95% CI = 1.47–2.22, $p < 0.001$) were observed in the obese group (Table 2).

When controlling for other demographic factors and the presence of cancer comorbidity, subjects with obesity continued to have higher odds of having diabetes with complications (OR = 1.91, 95% CI = 1.55–2.35, $p < 0.001$) and diabetes without complications (OR = 1.84, 95% CI = 1.43–2.38), $p < 0.001$] comorbidity (Table 3).

In addition, subjects with an older age were also observed to have higher odds of diabetes with complications (OR = 1.02, 95% CI = 1.02–1.03, $p < 0.001$) and diabetes without complications (OR = 1.03, 95% CI = 1.02–1.04, $p < 0.001$). Furthermore, subjects with cancer comorbidity had lower odds (OR = 0.56, 95% CI = 0.41–0.78, $p < 0.001$) and higher odds of having a Black or African American demographic (OR = 1.52, 95% CI = 1.08–2.15, $p = 0.017$) in diabetes without complications comorbidity group (Table 3).

Thrombosis-associated diagnostic codes

Of the thrombosis-associated diagnostic codes observed, none were associated with the obesity group. After dividing the cohort into no diabetes mellitus and diabetes, there continued to be no association with obesity (Tables 4 and 5).

Discussion

The main objective of this study was to use a multi-center EHR database to determine whether obese patients diagnosed with HIT had greater odds of select comorbidities and

Table 1. Demographic characteristics of non-obese and obese subjects diagnosed with heparin-induced thrombocytopenia.

	Not obese	Obese	Unadj *p*	Bonf adj *p*
Total subjects (*n*, %)	696 (44.0%)	887 (56.0%)	—	—
Age (mean years, SD)	61.48 ± 14.41	59.95 ± 13.61	0.008	0.221
Sex (*n*, %)			0.037	0.998
Female	293 (42.1%)	421 (47.5%)		
Male	402 (57.8%)	466 (52.5%)		
Race (*n*, %)			0.426	1.000
American Indian or Alaska Native	3 (0.4%)	3 (0.3%)		
Asian	10 (1.4%)	5 (0.6%)		
Black or African American	92 (13.2%)	122 (13.8%)		
Native Hawaiian or other Pacific Islander	1 (0.1%)	1 (0.1%)		
White	478 (68.7%)	634 (71.5%)		
Ethnicity (*n*, %)			0.14	1.000
Hispanic or Latino	50 (7.2%)	48 (5.4%)		
Not Hispanic or Latino	583 (83.8%)	772 (87.0%)		
Body mass index (mean kg/m^2, SD)	24.97 ± 3.48	36.79 ± 5.45	<0.001	<0.001
Deaths (*n*, %)	229 (32.9%)	300 (33.8%)	0.707	1.000
Central venous access (*n*, %)	120 (17.2%)	211 (23.8%)	0.001	0.040

Unadj *p*: unadjusted *p* value; Bonf adj *p*: Bonferroni adjusted *p* value.

Table 2. Selected Charlson comorbidities divided by non-obese and obese subjects.

	Non-obese		Obese		*p*-Value
	Prevalence	OR (95% CI)	Prevalence	OR (95% CI)	
Acquired immunodeficiency disease or human immunodeficiency virus	14 (2.0%)	1.00 (Reference)	27 (3.0%)		
Cancer (any malignancy)	144 (20.7%)	1.00 (Reference)	177 (20.0%)	0.956 (0.747, 1.22)	1.000
Cerebrovascular disease	212 (30.5%)	1.00 (Reference)	279 (31.5%)	1.05 (0.845, 1.30)	1.000
Congestive heart failure	337 (48.4%)	1.00 (Reference)	463 (52.2%)	1.16 (0.954, 1.42)	1.000
Diabetes with complications	117 (16.8%)	1.00 (Reference)	230 (25.9%)	1.73 (1.35, 2.22)	<0.001
Diabetes without complications	241 (34.6%)	1.00 (Reference)	434 (48.9%)	1.81 (1.47, 2.22)	<0.001
Metastatic solid tumor	78 (11.2%)	1.00 (Reference)	98 (11.0%)	0.984 (0.718, 1.35)	1.000
Myocardial infarction	200 (28.7%)	1.00 (Reference)	253 (28.5%)	0.99 (0.795, 1.23)	1.000
Peripheral vascular disease	285 (40.9%)	1.00 (Reference)	393 (44.3%)	1.15 (0.938, 1.40)	1.000
Renal disease	294 (42.2%)	1.00 (Reference)	440 (49.6%)	1.35 (1.10, 1.64)	0.076

thrombosis compared to non-obese HIT patients. Understanding the risk factors and outcomes of obese patients diagnosed with HIT is important, as it may serve to improve our risk stratification and diagnostic approach for this patient population that already has an increased likelihood of in-hospital complications, including HIT. We found that obese subjects with HIT had higher odds of having diabetes as a comorbidity, but similar odds of thrombosis were observed in the non-obese and obese groups.

Diagnosing HIT can be challenging. It requires a careful assessment of clinical findings and laboratory data.[29] Through the use of the 4Ts, diagnosis of this condition has improved as it identifies subjects that require further testing early.[7] However, medications or severe illnesses such as sepsis or malignancy also cause thrombocytopenia, increasing the difficulty of making the diagnosis.[29–31] Any additional data that contribute to the evaluation of HIT are essential to identify these patients sooner.

Obese subjects are known to develop HIT.[8,16] In this patient population, it has been suggested the presence of other comorbidities may contribute to the immune response that is associated with HIT.[8,31] Conditions such as diabetes may trigger platelet hyperactivity and an elevated PF4, potentially making it more likely that certain patient populations may develop HIT.[32] Thus, if a hospitalized obese patient presents with clinical findings consistent with HIT, it is possible that the patient has a high likelihood of having HIT and potentially developing severe complications such as thrombosis. While it is assumed that obese patients may have these diseases, especially diabetes mellitus, whether they are associated with increased odds of HIT have not been investigated to our knowledge. The two studies examining the impact of

Table 3. Multivariable analysis of the association of diabetes with and without complications with the presence of obesity, age, sex, race, and presence of any cancer comorbidity (any malignancy and metastatic solid tumor).

Variables	Diabetes with complications		Diabetes without complications	
	OR (95% CI)	*p*-Value	OR (95% CI)	*p*-Value
Obesity (Ref: non-obese)	1.91 (1.55, 2.35)	<0.001	1.84 (1.43, 2.38)	<0.001
Age	1.02 (1.02, 1.03)	<0.001	1.03 (1.02, 1.04)	<0.001
Sex (Ref: female)	1.00 (0.81, 1.22)	0.960	0.95 (0.74, 1.21)	0.657
Black or African American Race (Ref: white)	1.08 (0.80, 1.47)	0.621	1.52 (1.08, 2.15)	0.017
Other race (Ref: white)	0.82 (0.34, 1.99)	0.655	1.13 (0.40, 3.16)	0.820
Unknown race (Ref: white)	1.03 (0.77, 1.38)	0.847	0.88 (0.61, 1.28)	0.505
Cancer comorbidity (Ref: absent cancer comorbidity)	0.86 (0.67, 1.11)	0.251	0.56 (0.41, 0.78)	<0.001

Table 4. Thrombosis-associated international classification of diseases, 10th edition diagnostic codes divided by non-obese and obese subjects with heparin-induced thrombocytopenia.

Variables	Non-obese		Obese		Unadj *p*	Bonf adj *p*
	Prevalence	OR (95% CI)	Prevalence	OR (95% CI)		
Acute myocardial infarction	148 (21.3%)	1.00 (Reference)	207 (23.3%)	1.13 (0.887, 1.43)	0.332	1.000
Aortic and peripheral arterial embolism or thrombosis	110 (15.8%)	1.00 (Reference)	179 (20.2%)	1.35 (1.04, 1.75)	0.026	0.519
Transient cerebral ischemia	15 (2.2%)	1.00 (Reference)	31 (3.5%)	1.64 (0.88, 3.07)	0.132	1.000
Cerebral infarction	113 (16.2%)	1.00 (Reference)	141 (15.9%)	0.98 (0.74, 1.28)	0.890	1.000
Occlusion and stenosis of cerebral artery	10 (1.4%)	1.00 (Reference)	22 (2.5%)	1.74 (0.82, 3.71)	0.154	1.000
Occlusion or stenosis of precerebral arteries	40 (5.7%)	1.00 (Reference)	45 (5.1%)	0.876 (0.57, 1.36)	0.576	1.000

OR: odds ratio; 95% CI: 95% confidence interval; Unadj *p*: unadjusted *p* value; Bonf adj *p*: Bonferroni adjusted *p* value.

obesity in HIT diagnosis did not describe the comorbidities present.[8,16] Examining whether these comorbidities are consistently present in obese patients with HIT can allow further understanding and may inform future studies.

In our study, we found that obese subjects are diagnosed with HIT. These findings are consistent with other studies.[8,16] It also highlights that HIT should be considered in all hospitalized patients. It is unclear, however, why obese subjects are impacted (often more so than non-obese). Obese subjects may be hospitalized more.[18,19] Thus, obese subjects are potentially exposed to heparin more so than non-obese subjects. A further longitudinal study is needed to examine if repeated exposure to heparin (especially in patients who require repeated hospitalizations) may place certain patient populations at greater risk for HIT.

We also found that obese subjects had higher odds of diabetes mellitus, even when controlling for demographic factors and diagnoses associated with a hypercoagulable state. These results may not be surprising. Obese patients are at risk for developing diabetes mellitus.[33] It is theorized that pro-inflammatory proteins released by adipocytes lead to a chronic inflammatory state impacting glucose regulation.[34] These two linked conditions, termed diabesity, are rising in prevalence worldwide, are associated with various comorbidities, and may need to be regarded as a potential risk factor for the development of HIT. There are several reasons to consider this. Diabetic subjects, in general, make up approximately 25% of hospitalizations in the United States[35] and often require readmission.[36] Thus, exposure to heparin-based products and an immune response resulting in HIT may develop. It is also possible that diabetes may place obese subjects in a hypercoagulable state.[37] Thus, in addition to heparin exposure and the presence of thrombocytopenia, thrombosis may have formed (possibly due to the patient's obesity and diabetes). If this resulted in a higher pretest probability, after confirmation with HIT antibody and serotonin assay testing, this would have resulted in more obese diabetic subjects being diagnosed with HIT. Further study, thus, may be needed to specifically investigate the impact of diabetes mellitus and obesity when assessing the likelihood of HIT.

Our study also found that the odds of thrombosis were similar between the non-obese and obese groups. These findings could indicate that despite the potential hypercoagulable state of obesity, it is not as impactful as other risk factors (e.g., acute myocardial infarction, reduced mobility).[38] Deep

Table 5. Thrombosis-associated international classification of diseases, 10th edition diagnostic codes divided by no diabetes mellitus and diabetes in non-obese and obese subjects with heparin-induced thrombocytopenia.

	No diabetes mellitus					Diabetes mellitus				
	Non-obese	Obese	OR (95% CI)	Unadj *p*	Bonf adj *p*	Non-bese	Obese	OR (95% CI)	Unadj *p*	Bonf adj *p*
Acute myocardial infarction	77 (16.9%)	78 (17.2%)	1.02 (0.723, 1.44)	0.930	1.000	71 (29.5%)	129 (29.7%)	1.01 (0.717, 1.43)	1.000	1.000
Aortic and peripheral arterial embolism or thrombosis	73 (16.0%)	92 (20.3%)	1.33 (0.95, 1.87)	0.102	1.000	37 (15.4%)	87 (20.0%)	1.38 (0.907, 2.11)	0.147	1.000
Transient cerebral ischemia	8 (1.8%)	10 (2.2%)	1.26 (0.493, 3.23)	0.644	1.000	7 (2.9%)	21 (4.8%)	1.70 (0.712, 4.06)	0.314	1.000
Cerebral infarction	62 (13.6%)	59 (13.0%)	0.949 (0.647, 1.39)	0.845	1.000	51 (21.2%)	82 (18.9%)	0.868 (0.587, 1.28)	0.481	1.000
Occlusion and stenosis of cerebral artery	6 (1.3%)	11 (2.4%)	1.86 (0.683, 5.08)	0.233	1.000	4 (1.7%)	11 (2.5%)	1.54 (0.485, 4.89)	0.591	1.000
Occlusion or stenosis of precerebral arteries	19 (4.2%)	17 (3.8%)	0.895 (0.459, 1.74)	0.865	1.000	21 (8.7%)	28 (6.5%)	0.722 (0.401, 1.30)	0.282	1.000

OR: odds ratio; 95% CI: 95% confidence interval; Unadj *p*: unadjusted *p* value; Bonf adj *p*: Bonferroni adjusted *p* value.

vein thromboses and other thromboses, however, are associated with obesity in general.[39] It is possible that thrombosis is difficult to identify in obese subjects. Imaging studies may still be limited in obese subjects (especially when they may be done to screen for thrombosis).[40] Deep vein thrombosis symptoms may also be challenging to identify due to the difficulty in distinguishing between an acute edematous enlargement of an extremity due to venous obstruction or lymphedema due to retention of fluid by adipose tissue.[41,42] Finally, while obesity may be associated with deep vein thrombosis, thrombosis due to HIT may not be observed more in obese subjects. In a study conducted by Bloom et al.,[16] when the 4T score was compared between different weight groups, there was no statistical difference in the overall scores and scores that reached the high probability range (presuming this included thrombosis). Marler et al.[8] reported that only pulmonary embolus was statistically higher in the obese group, while other thromboses (specifically deep vein thrombosis, ischemic stroke, and myocardial infarction) were not significant. Further study is needed to determine why thrombosis is not higher in the obese group and whether further imaging or an alternative imaging strategy may be warranted to identify subjects with thrombosis.

Limitations

This study had several limitations. First, due to database limitations, no clinical documentation or imaging reports were available to review. We relied on diagnostic code entry to identify subjects with HIT, the comorbidities they had, and if thrombosis was a complication. Thus, the accuracy of the diagnostic codes utilized may be potentially subject to clinician bias, particularly HIT as clinicians may tend to overdiagnose this disease.[31] In addition, it is unknown whether there were other diagnoses and/or procedures present that were not coded. It is possible that other conditions, such as liver fibrosis (which can be present in obese patients), could impact the approach to HIT diagnosis.[43] This was not included in our study but should be considered in future studies. Our study only utilized argatroban as the non-heparin anticoagulant to identify this patient cohort. Thus, we may not have included subjects with HIT who were treated with other non-heparin anticoagulants and did not evaluate patients who may have been treated on an outpatient basis. Finally, limitations of this database prevented us from performing a closer examination of this patient population (including the dose and number of times a patient had previously received heparin).

Conclusions

Our study found that obese HIT subjects had higher odds of having comorbid diabetes mellitus, but did not have higher odds of thrombosis. Given obesity is considered a hypercoagulable state and potentially a risk factor for HIT, special

vigilance may be necessary to make the correct diagnosis. In addition, further study is needed to determine why obese patients diagnosed with HIT do not appear to suffer increased rates of thrombosis.

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None.

Authors' contributions

MD drafted the initial manuscript and approved the final manuscript as written. MD and CK conceptualized and designed the study and carried out the initial analyses. VW performed the statistical analysis, reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as written. AD reviewed and revised the manuscript for important intellectual content and approved the final manuscript as submitted. CK collected and organized the data, reviewed and revised the manuscript for important intellectual content, and approved the final manuscript as written.

Data availability statement

The data that support the findings of this study are available from TriNetX®. Restrictions apply to the availability of these data, which were used under license for this study.

Declaration of conflicting interests

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Ethics approval

Ethical approval for this study was obtained from the Penn State Health Institutional Review Board (IRB) (STUDY00020794)*.

Informed consent

Not applicable.

Trial registration

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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