Heparin Induced Thrombocytopenia in Patients with COVID-19

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Research

Keywords: Heparin Induced Thrombocytopenia, HIT, thrombosis, 4Ts score, HIT antibody testing, SRA, COVID-19

Posted Date: February 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-194846/v1

Version of Record: A version of this preprint was published at Blood on November 5th, 2020. See the published version at https://doi.org/10.1182/blood-2020-134702.

Abstract

Background

Acute respiratory and renal failure as well as systemic coagulopathy are critical aspects of the morbidity and mortality in patients with COVID-19. Heparin Induced Thrombocytopenia (HIT) occurs when IgG antibodies form against platelet factor 4-Heparin complex, resulting in platelet activation and removal, leading to a prothrombotic state. Studies have shown that only 6% who are investigated serologically for HIT actually have the diagnosis.

Methods

A retrospective analysis was performed on all COVID-19 positive patients hospitalized between March and June 2020. Patients with suspicion for HIT were tested for HIT antibodies with IgG-specific platelet factor 4(PF4)-dependent enzyme immunoassay (EIA). Confirmatory testing with serotonin release assay (SRA) and heparin-induced platelet aggregation were used in cases with intermediate or low optical density (OD) with EIA positivity (EIA+). Due to rarity of disease, a through literature review on HIT in COVID-19 patients was also analyzed.

Results

Incidence of EIA + in COVID-19 patients was 0.6%, significantly higher than in the general population 0.2% ($p < 0.0001$). The incidence of thromboembolic events in EIA + patients was 87.5%, significantly higher than the rate of 10.90% in all COVID-19 patients ($p < 0.0001$). The mortality rate in EIA + patients was 50%, significantly greater than the mortality rate of 12% in all hospitalized COVID-19 patients ($p = 0.0011$). Serological confirmation of HIT diagnosis was 37.5% which is significantly higher than confirmation of HIT in nonCOVID-19 patients 6% ($p < 0.0001$). Of 39 HIT antibody positive patients in the literature, 23.07% had positive confirmatory testing (6 SRA, 3 HIPAA) which is significantly higher than 5.6% in the general population ($p = 0.00001$). The incidence of thrombosis in EIA + COVID-19 patients in the literature was 56.4% which is significantly higher than reported rates of thrombotic events in in all COVID-19 patients in the literature at 4.8%[1] ($p = 0.00001$).

Conclusion

Our study indicates incidence of HIT is higher in the COVID-19 population. This can be attributed to the cytokine storm and severe sepsis seen in critically ill COVID-19 patients. Our study also suggests that development of HIT can contribute to increased risk for thromboembolic events as well as mortality of COVID-19 patients, however, our study is limited due to small sample size.

Key Points

- There is an increased risk of HIT in COVID-19 patients.
- Patients who are EIA+ or have serologically confirmed HIT have increased risk of thrombotic events and mortality.
- Diagnosing HIT in COVID-19 patients is complex due to difficulty in calculating 4Ts score and concern for possible inaccurate HIT testing in the setting of COVID-19 immune response and inflammation.
- COVID-19 patients who are treated with heparin-based products need to be carefully monitored for prompt diagnosis and treatment of HIT.

Introduction

The coronavirus disease 2019 (COVID-19) is a global pandemic caused by the novel coronavirus SARS-CoV-2. Initially identified in Wuhan, China in December 2019, COVID-19 has now caused over 1.7 million deaths worldwide.[2] Acute respiratory and renal failure as well as systemic coagulopathy are critical aspects of morbidity and mortality in patients with COVID-19.[1,3] Hematologic abnormalities such as elevated D-dimer, lymphopenia, elevated fibrinogen levels, increased prothrombin and partial thromboplastin times, and thrombocytopenia were reported in early studies.[4–6]

Thromboembolism including deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombotic events are common sequelae of COVID-19 infection, and are thought to be caused by a cytokine storm leading to endothelial injury and activation of circulating prothrombotic factors along with immobilization in critically ill patients.[7] Studies have reported incidence of VTE around 31% in this patient population.[8,9] Due to increased coagulopathy, intermediate to therapeutic dosing of thromboprophylaxis is recommended for all hospitalized COVID-19 patients.[10] Heparin based products such as unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are used due to anti-inflammatory and antiviral properties.[1,10,11] LMWH is preferred for COVID-19 patients due to decreased risk of bleeding, better response predictability, and decreased mortality rate.[11,12]

Many COVID-19 patients have prolonged hospital stays leading to extended duration of heparin exposure, which increases risk for heparin induced thrombocytopenia (HIT).[13,14] HIT occurs when IgG antibodies form against platelet factor 4-Heparin complex, resulting in platelet activation, subsequently leading to a prothrombotic state.[15,16] HIT is suspected when there is a platelet count decrease of more than 50% after 5–10 days of heparin exposure, along with evidence of hypercoagulability.[17] Current guidelines recommend testing patients for HIT based on 4T score of 4 or higher (points given for degree of thrombocytopenia, timing of heparin product therapy, thrombosis, and other causes of thrombocytopenia) to assess pretest probability of HIT.[18]

Initial clinical work up for HIT is performed by testing for HIT antibodies, but studies demonstrate that only 5.6% of those investigated serologically for HIT actually have confirmed diagnosis of HIT.[19] Functional assays like serotonin release assay (SRA) are more specific for HIT and identify only pathogenic antibodies to confirm HIT diagnosis.[20] Studies have shown that patients with optical density (OD) > 1 are likely to have positive SRA.[18] The use of unfractionated heparin, post-orthopedic and post-cardiac surgery state, female gender, need for renal replacement therapy (RRT), and older age are recognized as risk factors for HIT.[21] Treatment of HIT includes discontinuation of all heparin-based products and transitioning to a therapeutic dose of non-heparin anticoagulation. [14, 18]

This study was performed to analyze incidence, efficacy of testing, and adverse effects such as thrombosis and mortality associated with HIT in COVID-19 patients.

Methods

Patient and Data Collection

This study was approved by the Institutional Review Board (Approval #20042111-IRB03) on April 29, 2020. Patients who were over the age of 18 with confirmed COVID-19 infection by positive SARS-CoV2 reverse transcriptase polymerase chain reaction (RT-PCR) between March 1st, 2020 and June 26th, 2020 and hospitalized at Rush University System for Health Hospitals were included in the study. A database of patients that met these criteria was retrospectively extracted from our electronic medical record (EMR). Patient charts were reviewed by physicians to ensure accuracy of data.

Heparin Induced Thrombocytopenia

Patients with intermediate (score of 4-5) or high 4T score (6 or greater) for HIT, underwent IgG-specific platelet factor 4(PF4)-dependent enzyme immunoassay (EIA) testing. Washed platelet assays such as serotonin release assay (SRA) and heparin-induced platelet aggregation assay (HIPAA) were used as confirmatory tests in cases with intermediate (defined as OD of 1-2) or low OD (defined as .5-1) with EIA+. Cases with OD>1 or positive SRA were considered confirmatory for diagnosis of HIT. **Figure 1** describes selection of study cohort and **Table 1** describes EIA+ patient characteristics. EIA+ patients who were discharged from the hospital were contacted after 6 months for follow up.

Analysis

Incidence of HIT antibody positivity, thromboembolism, and mortality in EIA+ patients were compared to a control cohort of COVID-19 patients at our institution as well as the current reported literature on HIT. Demographic and subgroup analysis of risk factors for HIT was performed on EIA+ COVID-19 patients. Hospital courses for EIA+ patients were also studied to assess correlation of laboratory values and treatment on mortality.

Literature Review

Due to the rarity of this disease process, a thorough literature review on HIT in COVID-19 patients was done on December 1st, 2020. Fourteen case report studies were identified, and stipulations for inclusion included performance of HIT antibody testing (either antibodies to PF4 Heparin complex or latex immunoassay) and if patient specific data was reported. Patient data was extracted from studies to get patient information on COVID-19 HIT antibody positive patients (**Table 2**).

Statistical Analysis

SAS version 9.4 was used as a statistical software for analysis. Descriptive statistics were generated as counts and frequency for categorical variables and mean and standard deviation for continuous variables. Statistical analysis for categorical variables was done by using X^2 testing or Fisher's exact test when cell counts were small. T- tests were used for continuous variables. Proportions observed at Rush were compared to general population numbers by binomial proportion test.

Results

HIT Antibody Positivity

Out of the control cohort of 1265 hospitalized COVID-19 positive patients, 33 had intermediate to high 4T scores and were tested for HIT antibodies. In all COVID-19 patients who were tested for HIT, there was no difference in intermediate 4T scores predicting EIA+ at 26.1% compared to high 4T scores at 33.3% (p= 0.6248). EIA+ in COVID-19 patients with intermediate to high 4T scores at our institution was significantly higher at 24.24% compared to IgG EIA+ in the general population for intermediate to high 4T scores at 10.18% (p=0.00896).[16]

Of the 33 patients tested for HIT, only 8 patients were EIA+ (study cohort), with characteristics listed in **Table 1.** Incidence of EIA+ in COVID-19 patients was 0.6%, which is significantly higher than in the general population 0.2%[15] (p<0.0001, 95% CI 0.25-1.20%). Serological confirmation of HIT diagnosis in our study cohort was 37.5% which is significantly higher than confirmation of HIT in the general population 5.6%[16] (p<0.0001, 95% CI 29.57-85.32%). The mortality rate of the EIA+ study cohort was 50%, significantly greater than the mortality rate of 12% in COVID-19 patients in the control cohort (p=0.0011, CI 9.46-66.53).

Thrombosis Risk

The incidence of thromboembolic events in EIA+ patients in the study cohort was 87.5%, significantly higher than the rate of 10.90% in all COVID-19 patients in the control cohort (p<0.0001, CI 41.96- 86.98%). Of the EIA+ patients in the study cohort who had thrombosis, 28.57% had PE, 57.14% had DVT, 14.28% had a stroke. There was a statistically significant higher incidence of DVT in the study cohort compared to DVT in all COVID-19 patients in the control cohort 4.82% (p=0.0038). There was no difference in incidence of PE or stroke in EIA+ study cohort compared to PE (4.82%, p= 0.0557) or stroke (2.60%, p=0.1731) in all COVID-19 patients in the control cohort.

Hospital Course Analysis

There was no significant difference in demographic distribution between the study cohort of EIA+ patients and the control cohort of all COVID-19 hospitalized patients (**Table 3**). There was no difference in mortality rate of EIA+ patients based on demographics or risk factors for HIT (**Table 4**). The average days of anticoagulation received prior to HIT antibody testing was 6.75 days with standard deviation ± 6.43 days, and no difference in mortality rate based on days of anticoagulation before diagnosis of EIA+ (p=0.2362). In the EIA+ study cohort, 25% had exposure to both UFH and LMWH, 25% UFH only, 50% exposure to only LMWH. There was no difference in mortality rate for EIA+ COVID-19 patients based on the type of anticoagulation received, UFH 0%, LMWH 75%, Both 50% (p=0.6571). There was no difference in mortality rate between EIA+ patients who received prophylactic 50% or therapeutic dosage of anticoagulation 50% (p=1.0). After diagnosis with EIA+, 37.5% were transitioned to Argatroban and 62.5% were treated with Bivalirudin. There was no difference in mortality rate of patients who received Argatroban 33.3% compared to Bivalirudin 60% (p=1.0).

HIT antibody testing was sent on average 7.75 days into hospitalization with standard deviation ± 6.16 days. The hospital length of stay (LOS) of EIA+ study cohort patients was 27.9 days with standard deviation ± 7.66 days, which was significantly higher than all COVID-19 patients in the control cohort who had a mean hospital LOS of 9.836 with standard deviation of ± 10.27 days (p=0.0005, 95% CI 7.96 to 28.16).

Hematologic Laboratory Values Analysis

It was statistically significant that having severe thrombocytopenia (platelet count <50k) was not associated with increased mortality 0% whereas moderate thrombocytopenia (platelet count 50k-99k) was associated with increased mortality 100% (p=0.0286). The average days to platelet recovery in EIA+ patients was 6.29 days with standard deviation ± 3.45 days. There was no difference in mortality rate based on the number of days from diagnosis of EIA+ to platelet recovery (p=0.7383). The average highest D-dimer for all EIA+ patients was 14.34 times the upper limit of normal (ULN) with standard deviation of ± 8.52. There was no difference in mortality rate based on highest D-dimer level for EIA+ patients (p= 0.2917).

6 Month Follow up on Discharged EIA+ Patients

Of the 4 EIA+ patients who survived, one (25%) of those patients on follow up had died, increasing the overall mortality rate in the study cohort to 62.5%. This patient (Patient 6 on Table 1) had an acute myocardial infarction as well as hemorrhagic shock. Patient 3 from Table 1 suffered from dry gangrene. Patient 1 and patient 7 had no further complications.

Analysis based on Literature Review

There were 39 HIT antibody patients reported in the literature with HIT antibody testing and had patient specific data. Of those, 23.07% had positive confirmatory testing (6 SRA, 3 HIPAA) which is significantly

higher than 5.6%[16] in the general population (p=0.00001). The incidence of thrombosis in EIA+ COVID-19 patients in the literature was 56.4% which is significantly higher than reported rates of thrombotic events in in all COVID-19 patients in the literature at 4.8%[1] (p=0.00001). Of the EIA+ COVID-19 patients in the literature who reported both 4T scores and confirmatory testing, 0% of low 4Ts score were serologically positive, 44.44% of intermediate 4Ts score were serologically positive, and 37.5% of high 4Ts score were serologically positive with no significant difference of 4Ts score as a predictor for serologically positive HIT (p=0.5839).

Discussion

Our study investigated the impact of diagnosis of HIT on COVID-19 patients. We found a significantly higher incidence of HIT antibody positivity and serologically confirmed HIT in COVID-19 patients compared to nonCOVID-19 patients. Analysis of the current literature also showed higher incidence of serologically confirmed HIT in COVID-19 patients. This may be attributed to the increased exposure to heparin based thromboprophylaxis, increased hospital length of stay, and the hyperinflammation and heightened immune response in COVID-19 patients.[14, 22, 23]

Diagnosing HIT is complex and requires 4Ts score calculation, EIA testing, and functional assay testing like SRA.[18] Our data, supported by the literature analysis, showed that 4Ts score was not predictive of either EIA + or patient mortality. The viral disease process may lead to inconsistency in calculating 4Ts scores given the overlap in disease course between COVID-19 and HIT which includes previous exposure to heparin-based anticoagulation, new thrombosis, and thrombocytopenia.

Case reports in the literature describe concern for HIT in COVID-19 patients, but several studies omit confirmatory testing and identify very few patients with serologically confirmed HIT (Table 2). Riker et al reported 3 EIA + patients, one being SRA positive.[24] Lingamaneni et al describes one out of 5 EIA + patients with confirmed HIT and states suspicion for “overdiagnosis” of HIT in COVID-19 patients.[25] Another report by May et al noted 7 EIA + patients with one SRA confirmed HIT diagnosis. These findings were attributed to EIA testing detecting all anti- PF4/Heparin antibodies and the potential for false positive EIAs due to increased inflammation and immunoreactivity in COVID-19, leading to production of anti-PF4/heparin antibodies that are nonpathogenic for HIT.[26]

It is unclear how to accurately diagnose HIT in COVID-19 patients due to varying sensitivity and specificity between different EIA and confirmatory tests.[27] Even with our institution’s highly sensitive and specific IgG EIA test, 62.5% patients who were confirmatory testing negative. It has been speculated that the heterogeneity of HIT antibodies, differing in size, affinity, and specificity, may affect their ability to activate platelets, endothelial cells, and leukocytes which may also contribute to variations in pathogenicity of HIT.[28] The hyperinflammatory environment caused by COVID-19 may also alter the structure of HIT antibodies in a way that retains their pathologic properties but helps evade detection by confirmatory testing. Even with confirmatory testing, there is evidence of SRA negative HIT as well as

spontaneous HIT that should be taken into account when there is a clinical picture concerning for HIT.[13, 27] Emerging literature also recommends SRA negative blood samples with high clinical suspicion for HIT be sent for PF4-dependent platelet activation assays like SPF4-SRA.[14]

Given discordance in testing for HIT in COVID-19, there is still a question on whether we should be treating for HIT in this population based on high clinical suspicion. Studies have shown that presence of EIA + in certain clinical settings can be a prognostic factor for adverse events, even without clinical evidence of HIT and could be a surrogate marker for inflammation.[20] This could be clinically significant in COVID-19 especially as current and future COVID-19 treatments become available and specifically target the inflammatory state.

The increased mortality rate of EIA + in COVID-19 patients may be attributed to increased thrombotic rates and severity of COVID-19 disease in this cohort, and all 8 patients had severe COVID-19 disease per institutional guidelines with ICU admission, mechanical ventilation requirement, and acute renal failure. Our analysis also showed increased mortality in EIA + patients who had moderate thrombocytopenia over both severe and mild thrombocytopenia, with moderate thrombocytopenia being more common in patients with HIT.[18]

Limitations of our study cohort include a small sample size, which increases risk for skewed analysis and limited information that can be reasonably inferred from our data. Despite our small sample size, our study is currently the largest sample of EIA + patients reported at a single institution and the only one with analysis done to better understand the consequences of HIT on COVID-19. Our analysis of EIA + COVID-19 patients reported in the literature yielded similar results to our data which supports the validity of our findings. Following completion of our initial data analysis in June 2020, we re-extracted data in November of 2020 to look for additional COVID-19 patients with HIT, and found one additional patient who was EIA + and SRA negative. To better understand overall association with HIT in this population, a multi-institutional collaboration needs to be done to increase sample size due to rarity of HIT in COVID-19.

Conclusion

In conclusion, our study showed increased incidence, thromboembolic events, and mortality of EIA + and serologically confirmed HIT in hospitalized patients with COVID-19. Due to challenges with 4Ts scoring in COVID-19 patients, we raise the notion of re-evaluating how to assess pre-test probability screening in this population and speculate that incorporating high clinical suspicion may help identify and treat HIT in COVID-19 patients. The COVID-19 disease process may affect EIA and confirmatory testing which makes diagnosing HIT in this population complex. EIA + COVID-19 patients had higher incidence of thrombosis, which was also replicated in our literature analysis of EIA + COVID-19 patients. This could be in part due to both COVID-19 and HIT causing pro-inflammatory states leading to release of tissue factor and activation of thrombin, resulting in a prothrombotic state.[29] EIA + was predictive of a poorer prognosis including increased thrombosis, mortality, hospital LOS, and could be considered as an inflammatory

marker in COVID-19 patients. The increased incidence of serologically confirmed HIT indicates that anticoagulation with heparin-based products and escalation of anticoagulation dosing should be done with caution, and patients should be carefully monitored for signs of HIT. Prospective studies and randomized control trials are needed to better understand diagnosis and treatment of EIA + and serologically confirmed HIT in COVID-19 patients in order to improve morbidity and mortality associated with both disease processes.

Declarations

Author Contribution:

1. Warrior contributed to writing the first draft of the manuscript, study concept and design, literature review, data collection, data analysis, creation of tables and figures, critical revision of the manuscript, and final approval.
2. Behrens contributed to study concept and design, literature review, creation of tables, writing and critical revision of the manuscript, and final approval.
3. Gezer and P. Venugopal contributed to critical revision of the manuscript and final approval.
4. Jain contributed to study concept and design, thorough mentorship and guidance through research process, critical revision of the manuscript, and final approval.

Acknowledgements:

The authors would like to acknowledge Ekta Kishen for her contribution to data extraction and Todd Beck for his help with statistical analysis of our data.

Foot Notes:

For original data please contact Surbhi Warrior (Surbhi_warrior@rush.edu).

References

1. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. *Blood*. Jul 23 2020;136(4):489-500. doi:10.1182/blood.2020006520
2. Johns Hopkins University.
3. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. *JAMA Intern Med*. Jul 1 2020;180(7):934-943. doi:10.1001/jamainternmed.2020.0994
4. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. Apr 30 2020;382(18):1708-1720. doi:10.1056/NEJMoa2002032

5. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. Feb 15 2020;395(10223):497-506. doi:10.1016/s0140-6736(20)30183-5
6. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. *Ann Hematol*. Jun 2020;99(6):1205-1208. doi:10.1007/s00277-020-04019-0
7. Singhania N, Bansal S, Nimmatoori DP, Ejaz AA, McCullough PA, Singhania G. Current Overview on Hypercoagulability in COVID-19. *Am J Cardiovasc Drugs*. Oct 2020;20(5):393-403. doi:10.1007/s40256-020-00431-z
8. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. Jul 2020;191:145-147. doi:10.1016/j.thromres.2020.04.013
9. Trigonis RA, Holt DB, Yuan R, et al. Incidence of Venous Thromboembolism in Critically Ill Coronavirus Disease 2019 Patients Receiving Prophylactic Anticoagulation. *Crit Care Med*. Sep 2020;48(9):e805-e808. doi:10.1097/ccm.0000000000004472
10. Barnes GD, Burnett A, Allen A, et al. Thromboembolism and anticoagulant therapy during the COVID-19 pandemic: interim clinical guidance from the anticoagulation forum. *J Thromb Thrombolysis*. Jul 2020;50(1):72-81. doi:10.1007/s11239-020-02138-z
11. Buijsers B, Yanginlar C, Maciej-Hulme ML, de Mast Q, van der Vlag J. Beneficial non-anticoagulant mechanisms underlying heparin treatment of COVID-19 patients. *EBioMedicine*. Sep 2020;59:102969. doi:10.1016/j.ebiom.2020.102969
12. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. May 2020;18(5):1094-1099. doi:10.1111/jth.14817
13. Liu X, Zhang X, Xiao Y, et al. Heparin-induced thrombocytopenia is associated with a high risk of mortality in critical COVID-19 patients receiving heparin-involved treatment. medRxiv; 2020.
14. Warkentin TE, Kaatz S. COVID-19 versus HIT hypercoagulability. *Thromb Res*. Dec 2020;196:38-51. doi:10.1016/j.thromres.2020.08.017
15. Greinacher A. CLINICAL PRACTICE. Heparin-Induced Thrombocytopenia. *N Engl J Med*. Jul 16 2015;373(3):252-61. doi:10.1056/NEJMcp1411910
16. Greinacher A, Juhl D, Strobel U, et al. Heparin-induced thrombocytopenia: a prospective study on the incidence, platelet-activating capacity and clinical significance of antiplatelet factor 4/heparin antibodies of the IgG, IgM, and IgA classes. *J Thromb Haemost*. Aug 2007;5(8):1666-73. doi:10.1111/j.1538-7836.2007.02617.x
17. Greinacher A. Heparin-Induced Thrombocytopenia. *N Engl J Med*. Nov 5 2015;373(19):1883-4. doi:10.1056/NEJMc1510993
18. Warkentin TE. Heparin-induced thrombocytopenia: diagnosis and management. *Circulation*. Nov 2 2004;110(18):e454-8. doi:10.1161/01.Cir.0000147537.72829.1b
19. Warkentin TE. HIT paradigms and paradoxes. *J Thromb Haemost*. Jul 2011;9 Suppl 1:105-17. doi:10.1111/j.1538-7836.2011.04322.x

20. Warkentin TE, Sheppard JA. Testing for heparin-induced thrombocytopenia antibodies. *Transfus Med Rev*. Oct 2006;20(4):259-72. doi:10.1016/j.tmrv.2006.05.001
21. Kato S, Takahashi K, Ayabe K, et al. Heparin-induced thrombocytopenia: analysis of risk factors in medical inpatients. *Br J Haematol*. Aug 2011;154(3):373-7. doi:10.1111/j.1365-2141.2011.08746.x
22. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical Characteristics of Covid-19 in New York City. *N Engl J Med*. Jun 11 2020;382(24):2372-2374. doi:10.1056/NEJMc2010419
23. Paparella D, Scrascia G, Galeone A, et al. Formation of anti-platelet factor 4/heparin antibodies after cardiac surgery: influence of perioperative platelet activation, the inflammatory response, and histocompatibility leukocyte antigen status. *J Thorac Cardiovasc Surg*. 2008/12// 2008;136(6):1456-1463. doi:10.1016/j.jtcvs.2008.06.014
24. Riker RR, May TL, Fraser GL, et al. Heparin-induced thrombocytopenia with thrombosis in COVID-19 adult respiratory distress syndrome. *Res Pract Thromb Haemost*. Jul 2020;4(5):936-941. doi:10.1002/rth2.12390
25. Lingamaneni P, Gonakoti S, Moturi K, Vohra I, Zia M. Heparin-Induced Thrombocytopenia in COVID-19. *J Investig Med High Impact Case Rep*. Jan-Dec 2020;8:2324709620944091. doi:10.1177/2324709620944091
26. May JE, Siniard RC, Marques M. The challenges of diagnosing heparin-induced thrombocytopenia in patients with COVID-19. *Res Pract Thromb Haemost*. Aug 2 2020;4(6):1066-7. doi:10.1002/rth2.12416
27. Warkentin TE, Nazy I, Sheppard JI, Smith JW, Kelton JG, Arnold DM. Serotonin-release assay-negative heparin-induced thrombocytopenia. *Am J Hematol*. Jan 2020;95(1):38-47. doi:10.1002/ajh.25660
28. Walenga JM, Jeske WP, Prechel MM, Bakhos M. Newer insights on the mechanism of heparin-induced thrombocytopenia. *Semin Thromb Hemost*. Feb 2004;30 Suppl 1:57-67. doi:10.1055/s-2004-823004
29. Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. May 2 2020;395(10234):1417-1418. doi:10.1016/s0140-6736(20)30937-5
30. Daviet F, Guervilly C, Baldesi O, et al. Heparin-Induced Thrombocytopenia in Severe COVID-19. *Circulation*. Nov 10 2020;142(19):1875-1877. doi:10.1161/circulationaha.120.049015
31. Patell R, Khan AM, Bogue T, et al. Heparin induced thrombocytopenia antibodies in Covid-19. *Am J Hematol*. Jul 13 2020;doi:10.1002/ajh.25935
32. Ogawa Y, Nagata T, Akiyama T, et al. Argatroban therapy for heparin-induced thrombocytopenia in a patient with coronavirus disease 2019. *J Thromb Thrombolysis*. Nov 2020;50(4):1012-1014. doi:10.1007/s11239-020-02248-8
33. Huang CT, Hsu SY, Chang KW, Huang CG, Yang CT, Cheng MH. Heparin-induced thrombocytopenia and thrombosis in a patient with Covid-19. *Thromb Res*. Dec 2020;196:11-14. doi:10.1016/j.thromres.2020.07.056
34. Turshudzhyan A. SARS-CoV2 induced pulmonary embolism and complications from anticoagulation. *Respir Med Case Rep*. 2020;31:101176. doi:10.1016/j.rmcr.2020.101176

35. Lozano R, Franco ME. Incidence of heparin-induced thrombocytopenia in patients with 2019 coronavirus disease. *Med Clin (Barc)*. Nov 13 2020;155(9):409-410. Incidencia de trombocitopenia inducida por heparina en pacientes con enfermedad por coronavirus 2019. doi:10.1016/j.medcli.2020.05.041
36. Bidar F, Hékimian G, Martin-Toutain I, Lebreton G, Combes A, Frère C. Heparin-induced thrombocytopenia in COVID-19 patients with severe acute respiratory distress syndrome requiring extracorporeal membrane oxygenation: two case reports. *J Artif Organs*. Aug 12 2020;doi:10.1007/s10047-020-01203-x
37. Dragonetti D, Guarini G, Pizzuti M. Detection of anti-heparin-PF4 complex antibodies in COVID-19 patients on heparin therapy. *Blood Transfus*. Jul 2020;18(4):328. doi:10.2450/2020.0164-20
38. Parzy G, Daviet F, Puech B, et al. Venous Thromboembolism Events Following Venovenous Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Syndrome Coronavirus 2 Based on CT Scans. *Crit Care Med*. Oct 2020;48(10):e971-e975. doi:10.1097/ccm.0000000000004504
39. Tran M, Sheth C, Bhandari R, Cameron SJ, Hornacek D. SARS-CoV-2 and pulmonary embolism: who stole the platelets? *Thromb J*. 2020;18:16. doi:10.1186/s12959-020-00229-8

Tables

Table 1: EIA Positive Patient Characteristics:

HIT Antibody Positive Patient Information																
	Demographics					Risk Factors					Hospital Course					
Patient	Sex	Race	BMI	Age	AC	HX of Surgery or Cancer	RRT	OD	Confirmatory Test	Platelet Nadir	Peak D-Dimer	Thrombotic Event	Bleeding Event	COVID-19 Treatment	AC After EIA+	Death
1	F	Black	25.4	80	UFH	Cancer	No	1.31		40	5.60	DVT	No	None	Bivalirudin	No
2	M	Hispanic	29.8	63	LMWH/UFH	No	Yes	0.62	SRA Positive	67	14.85	PE	No	Steroids	Argatroban	Yes
3	M	White	32.2	74	UFH	No	No		HIPAA Negative	127	8.68	DVT	No	Steroids	Bivalirudin	No
4	M	Hispanic	34.7	31	LMWH	Cancer	No	1.99		82	>27.5	PE	No	Remdesivir/Hydroxychloroquine	Argatroban	Yes
5	M	Hispanic	27.2	58	LMWH	No	No	1.68	SRA Negative	60	17.24	DVT	No	Remdesivir/Steroids	Argatroban	Yes
6	M	Black	20.6	77	LMWH/UFH	No	Yes	0.7	SRA Negative	28	>27.5	Stroke	ICH	None	Argatroban	No
7	M	Hispanic	32.8	36	LMWH	Cardiac Surgery	No	0.88	SRA Negative	2	9.02	No	No	Steroids	Argatroban	No
8	M	White	33.2	34	LMWH	No	No		SRA Negative	65	14.29	DVT	Chest tube bleed	Remdesivir/Steroids/Tocilizumab	Bivalirudin	Yes

* AC - Anticoagulation, *BMI - Body Mass Index, RRT - Renal Replacement Therapy, *OD- Optical Density, *SRA- Serotonin Release Assay, *HIPAA- Platelet Aggregation Assay,*LMWH - Low Molecular Weight Heparin, *DVT - Deep Vein Thrombosis, *PE - Pulmonary Embolism, *ICH- Intracranial Hemorrhage

Table 2: COVID-19 HIT Literature overview[24-26, 30-39]

Author, Date	Age	Gender	AC Type Before c/f HIT	AC Dose Before c/f HIT	Days After Initiation AC HIT Suspected	Platelet Nadir	New Thrombosis Y/N	Thrombosis Type	4Ts Score	HIT Ab+ Y/N	Screening Test Used	Confirmatory Test	Confirmatory Test Y/N	AC after c/f HIT	Bleeding Events	COVID-19 Related Treatment	Mortality
Lingamaneni et al, July 2020	63	M	LMWH then UFH	Therapeutic	11	96	Y	DVT	6	Y	PF4/Hep Ab	SRA	Y	Argatroban	N		Y
	63	M		Therapeutic	6		Y	DVT	7	Y	PF4/Hep Ab	SRA	N	Argatroban			
	70	F		Therapeutic	8		Y	DVT	7	Y	PF4/Hep Ab	SRA	N	Argatroban			
	46	F		Therapeutic	2		Y	Suspected PE	4	Y	PF4/Hep Ab	SRA	N	Argatroban			
	53	M		Therapeutic	7		N		5	Y	PF4/Hep Ab	SRA	N	Argatroban			
Riker et al, May 2020	70	M	UFH	Ppx	13	90	Y	PE	6	Y	PF4/Hep Ab	SRA	Y	Bivalirudin		HCQ, Toci, Remdesivir	Y
	74	M	UFH	Therapeutic	9	87	Y	DVT	4	Y	PF4/Hep Ab	SRA	N	Fondiparinux	Y	Steroids	Y
	53	M	UFH	Therapeutic	11	22	N	Skin Necrosis	6	Y	PF4/Hep Ab	SRA	N	Argatroban		HCQ	
Daviet et al, Sept 2020	46	M	LMWH then UFH	Therapeutic	16	33	Y	DVT (multiple)	6	Y	PF4/Hep Ab			Argatroban		HCQ	N
	50	M	LMWH then UFH	Therapeutic	13	73	Y	Intracardiac thrombosis, ECMO membrane thrombosis	6	Y	PF4/Hep Ab			Argatroban		HCQ	N
	43	F	LMWH then UFH	Therapeutic	15	48	Y	DVT (multiple), ECMO pump thrombosis	6	Y	PF4/Hep Ab			Argatroban		Lopinavir/Ritonavir	N
	63	M	LMWH then UFH	Therapeutic	14	56	Y	Stroke	4	Y	PF4/Hep Ab			Danaparoid		HCQ	N
	59	M	LMWH then UFH	Therapeutic	9	62	Y	DVT	5	Y	PF4/Hep Ab			Danaparoid			N
	57	M	UFH	Therapeutic	11	39	N		5	Y	PF4/Hep Ab			Danaparoid		HCQ	N
	69	M	UFH	Therapeutic	16	107	N		4	Y	PF4/Hep Ab			Danaparoid		HCQ	N
Patell et al, July 2020	68	F	UFH	Therapeutic	7	<5	N		4	Y	LIA for PF4 Ab	SRA	Y	Argatroban	Y		Y (3 Deaths in Study)
	71	F	UFH	Therapeutic	6	47	N		6	Y	LIA for PF4 Ab	SRA	N	Argatroban	Y		
	65	M	UFH	Therapeutic	6	51	Y	Stroke, Splenic Infarets	8	Y	LIA for PF4 Ab	SRA	Y	Argatroban	Y		
	49	M	UFH	Therapeutic	12	25	N		6	Y	LIA for PF4 Ab	SRA	Y	Argatroban			
	82	M	UFH	Therapeutic	14	132	N		5	Y	LIA for PF4 Ab			Bivalirudin			
May et al, July 2020	50	M	UFH	Therapeutic		49	N		5	Y	PF4/Hep Ab ELISA	SRA	N				Y
	79	F	LMWH	Ppx		155	N		3	Y	PF4/Hep Ab ELISA	SRA	N				N
	58	F	LMWH	Ppx		305	Y	PE	3	Y	PF4/Hep Ab ELISA	SRA	N				Y
	61	F	UFH	Therapeutic		37	N		4	Y	PF4/Hep Ab ELISA		Y				
	38	M	LMWH then UFH	Therapeutic		39	N		3	Y	PF4/Hep Ab ELISA	SRA	N				
	71	F	UFH	Therapeutic		70	Y	Stroke	6	Y	PF4/Hep Ab ELISA	SRA	N				Y
	46	M	LMWH	Ppx		59	Y	DVT	5	Y	PF4/Hep Ab ELISA	SRA	N				
Ogawa et al, August 2020	37	M	UFH	Therapeutic	15	~50	Y	PE	6	Y	LIA for PF4 Ab			Argatroban	Y		N
Huang et al, August 2020	44	M	UFH	Therapeutic	12	80	N		6	Y	PF4 Ab ELISA				Y	HCQ	Y
Turshudzhyan, July 2020	69	F	UFH	Therapeutic	15	22	Y	PE		Y	PF4/Hep Ab			Argatroban	Y	HCQ, Azithromycin, Toci, Steroids	
Bidar et al, August 2020	62	F	UFH	Therapeutic	16	29	N			Y	PF4/Hep Ab	HIPA	Y	Argatroban	N		
	38	M	UFH	Therapeutic	16	93	Y	ECMO Circuit		Y	PF4/Hep Ab	HIPA	Y	Argatroban	N		
Dragonetti et al, May 2020	77	F	UFH			49				Y	LIA for PF4 Ab			Fondiparinux			
	70	M	UFH			64				Y				Fondiparinux			
	73	M	UFH			58				Y				Fondiparinux			
Parzy et al, June 2020			UFH	Therapeutic			Y	DVT & Oxygenator Thrombosis		Y	PF4/Hep Ab	Platelet Aggregation		Argatroban			
			UFH	Therapeutic			Y	DVT & Pump Thrombosis		Y				Argatroban			
			UFH	Therapeutic			Y	DVT		Y				Argatroban			
Tran et al, Sept 2020	62	M	LMWH then UFH	Therapeutic	16	91	Y	PE	4	Y	PF4/Hep Ab ELISA	HIPA	Y	Bivalirudin		HCQ, Convalescent plasma	

Abbr: AC- Anticoagulation, UFH- Unfractionated Heparin, LMWH- Low Molecular Weight Heparin, Ppx- Prophylactic, Toci- Tocilizumab, HCQ- Hydroxychloroquine, LIA- Latex Immunoassay, Ab- Antibody

Table 3: EIA+ COVID-19 Study Cohort Patient Demographics Compared to COVID-19 Control Cohort Patient Demographics

Demographic	EIA+ COVID-19	All COVID-19	P value
Gender			
Female	12.50%	44.22%	p= 0.0852
Male	87.50%	55.77%	p= 0.0852
Race			
African American	25%	37.80%	p= 0.7175
White	25%	12.79%	p= 0.2751
Hispanic	50%	43.30%	p= 0.7332
Other	0%	6.11%	p= 1.0
BMI			
Normal <25	12.50%	35.98%	p= 0.2716
Overweight 25-35	37.50%	28.90%	p= 0.4201
Obese >35	50%	35.12%	p= 1.0
Age			
Young <45	37.50%	23.50%	p= 0.4017
Middle aged 45-65	25%	43.99%	p= 0.4778
Elderly >65	37.50%	32.51%	p= 0.7200

*BMI- Body Mass Index

Table 4: EIA+ COVID-19 Patients Effects on Mortality Analysis

Patient Characteristic	Mortality Rate of Patients with Characteristic	Analysis Between Characteristic
Risk Factors		
Surgery	0%	
Malignancy	50%	
RRT	50%	p=1.0
Type of Anticoagulation		
UFH and LMWH	50%	
UFH	0%	
LMWH	75%	p= 0.3143
Dose of Anticoagulation		
Prophylactic	50%	
Therapeutic	50%	p= 1.0
Anticoagulation after HIT		
Argatroban	60%	
Bivalirudin	33%	p= 1.0
COVID-19 Treatment		
Remdesivir	100%	
Tocilizumab	100%	
Hydroxychloroquine	100%	
Steroids	60%	p= 0.6667
Type of Thrombosis		
PE	100%	
DVT	50%	
Stroke	0%	p= 0.4286
Gender		
Male	57.14%	
Female	0%	p=1.0
Race		
African American	0%	
Hispanic	75%	
Caucasion	50%	p=0.3143
BMI		
Normal <25	0%	
Overweight 25-30	66.67%	
Obese >30	50%	p= 0.7429
Age		
young <45	66%	
middle aged 45-65	100%	
elderly >65	0%	p=0.1000

Figures

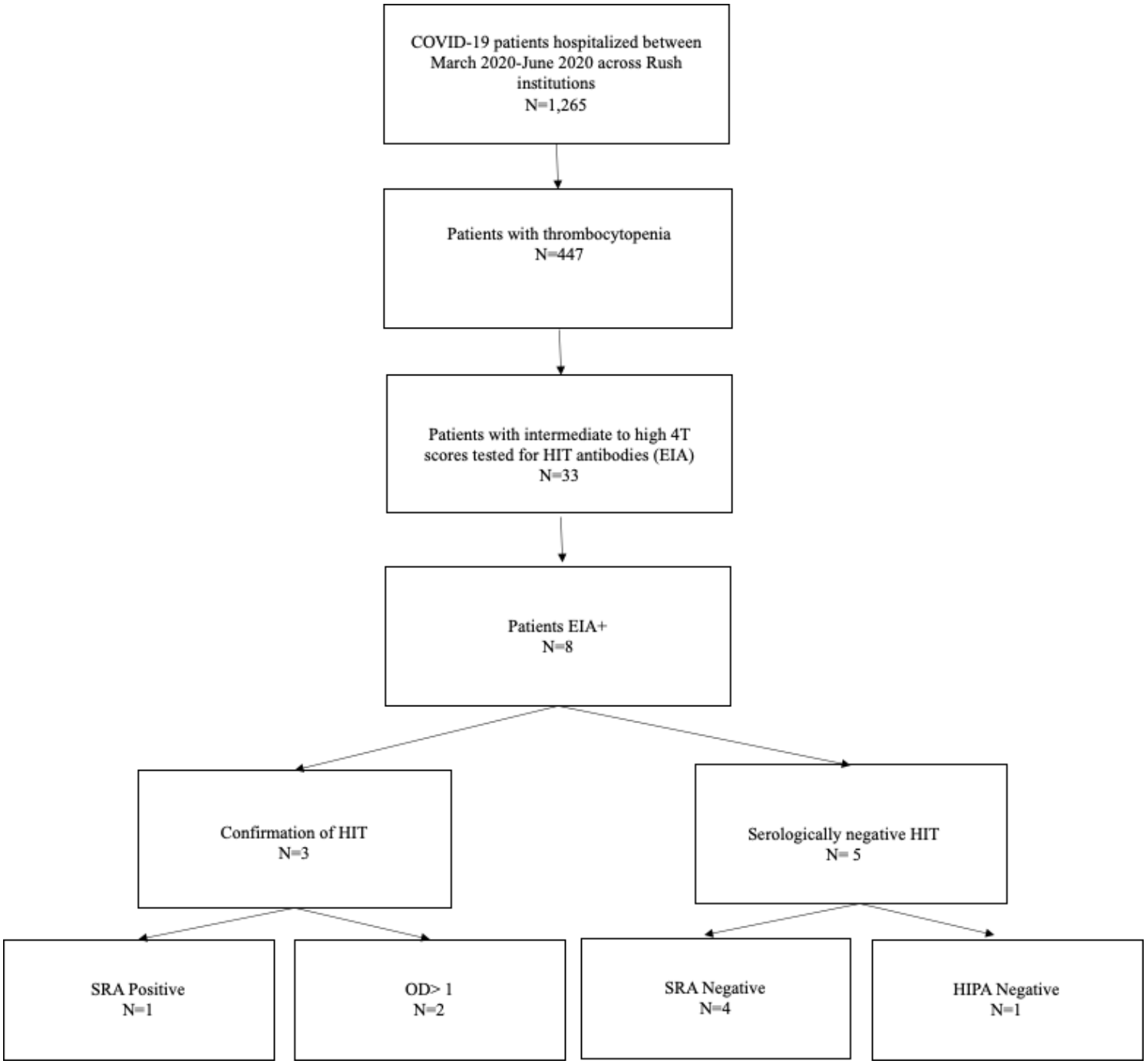

Figure 1

Inclusion Criteria Chart