ORIGINAL ARTICLE

Heparin-induced thrombocytopenia in end-stage renal disease: Reliability of the PF4-heparin ELISA

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Abstract

Background: Diagnosing heparin-induced thrombocytopenia (HIT) in patients with end-stage renal disease (ESRD) can be difficult, as they are frequently exposed to heparin and have multiple etiologies for thrombocytopenia.

Objective: To correlate 4T scores, IgG heparin–platelet factor 4 (PF4-heparin) ELISA results, and serotonin release assay (SRA) results in patients with ESRD.

Methods: We performed a retrospective review of patients with ESRD (creatinine clearance < 15 mL/min or on renal replacement therapy [RRT]) who underwent PF4-heparin ELISA testing from October 2015 to September 2019. True-positive PF4s required an intermediate to high 4T score (≥4), a positive SRA, and receipt of treatment for a HIT diagnosis. False-positive PF4s were defined as a positive PF4 with a negative SRA, low 4T score (<4), or lack of treatment for HIT. Indeterminant cases were classified on the basis of clinical assessment by the treating team (eg, hematology or vascular medicine).

Results: Of 254 patients with ESRD (92% on RRT), 29 patients (11.4%) had a positive PF4. Eleven (37.9%) had a confirmed diagnosis of HIT: 10 patients who met all of the above criteria, and one who met the 4T criteria and was treated for HIT but did not have SRA testing due to high clinical suspicion and a positive PF4 test. False-positive PF4 values occurred in 8 patients (27.5%). Of 10 (34.5%) indeterminant cases of patients with a negative SRA but intermediate to high 4T and positive PF4, only 3 patients were treated for HIT, whereas the other 7 were judged not to have HIT as assessed by the treating clinician. In patients with an intermediate to high 4T score and PF4 optical density > 0.4 but negative SRA, who were not treated for HIT, there were no adverse outcomes documented such as new or progressive thrombosis.

Conclusion: In our ESRD population, 4T scores and PF4 testing were not predictive of a clinical diagnosis of HIT.

Essentials

- Diagnosing heparin-induced thrombocytopenia (HIT) in patients with end-stage renal disease (ESRD) is often challenging.
- We conducted a retrospective analysis of 254 patients with an IgG heparin–platelet factor 4 (PF4) ELISA test.
- Of 29 patients with positive PF4s, 8 (27.6%) were classified as false positive.
- 4T scores and PF4 testing may not be accurate to assess for HIT in the ESRD population.

1 | INTRODUCTION

Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) have been cornerstones of therapy for the treatment and prevention of thromboembolism for decades.[1] Despite the many advantages of using heparin or LMWH in the treatment and prevention of thrombosis, one major limitation is the development of heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated adverse drug reaction caused by the development of platelet-activating antibodies that target the platelet factor 4 (PF4)–heparin complexes, leading to a decline in platelets and paradoxically resulting thrombosis in severe cases.[2] A diagnosis of HIT is made on the basis of an assessment of the clinical presentation using a validated pretest probability score (eg, 4Ts score) in combination with laboratory corroboration with an antigen assay (eg, IgG PF4 ELISA) and/or a functional assessment with a platelet-activating assay (eg, serotonin release assay [SRA]).[3]

Patients with end-stage renal disease (ESRD) may have many exposures to heparin products over their lifetime due to an increased risk of thrombosis, even more so for patients managed with dialysis.[4] For patients with ESRD who have been exposed to heparin, new-onset thrombocytopenia can be difficult to evaluate due to multiple potential etiologies for thrombocytopenia. In addition to causes of thrombocytopenia that apply to the general population such as drug-induced, infection, hemodilution, and hematologic disorders, causes of thrombocytopenia in patients with ESRD may include increased platelet consumption, decreased platelet production and function, platelet destruction from interaction with dialysis catheters, immunosuppression, uremia, and comorbidities such as diabetes.[5–7] In addition to the difficulty in diagnosing HIT using validated pretest probability scores in this population, antigen tests may also overestimate the number of patients with confirmed HIT by identifying IgG PF4-heparin antibodies that are not causing pathologic platelet activation. In patients with renal disease, the prevalence of HIT antibodies may overestimate the number of patients with pathogenic antibodies that result in platelet activation and increased risk of thrombosis.[8–11] While the exact incidence of HIT with thrombosis in ESRD is unknown, one large, observational study determined an incidence of 0.26 per 100 patients in their cohort of 13 682 patients.[12] There is also a chance for a false-negative SRA with an estimated specificity of 98% and a sensitivity of 95%;

therefore, clinical judgment is crucial in determining whether to treat for HIT.[13,14] It is also important to note that specificity and sensitivity vary by laboratory.

Based on previous data from our institution, we found that the PF4-heparin ELISA IgG test has a specificity of 93.5% and a sensitivity of 95.8%.[14] In our ESRD population, we have observed a higher-than-anticipated number of patients that have an intermediate to high 4T score, a positive IgG PF4-heparin ELISA result but a negative SRA. The aim of this analysis is to evaluate 4T scores, PF4-heparin ELISA results, and SRA in patients with ESRD.

2 | METHODS

This was a single-center, retrospective review of patients at Brigham and Women's Hospital (BWH), approved by the Massachusetts General Brigham's Institutional Review Board. All patients admitted to BWH with a PF4-heparin IgG ELISA test (Lifecodes PF4 IGG assay; Immucor, Norcross, GA, USA) between October 2015 and September 2019 were included. Patients with an available PF4 result were identified using a Research Patient Data Registry. Patients were excluded from the analysis if they were <18 years of age or if they did not have ESRD. ESRD was defined as having a creatinine clearance (CrCl) < 15 mL/min or receiving renal replacement therapy (RRT). RRT included continuous venovenous hemofiltration (CVVH), hemodialysis (HD), and peritoneal dialysis (PD).

Baseline characteristics, type of heparin product, route of administration, type of RRT, calculated 4T scores, PF4 results, and SRA (Versiti, Milwaukee, WI, USA) results were collected. We used the validated 4T assessment score that categorizes the pretest probability of HIT as low (0-3 points, ≤5% probability of HIT), moderate (4-5 points, ≈14% probability of HIT), and high (6-8 points, ≈64% probability of HIT).[2] If a 4T score was documented in the patient chart, it was confirmed by the study team based on review of data in the medical record. If a 4T score was not documented in the patient chart, our study team calculated a 4T score based on data in the medical record. The institutional cutoff for a positive IgG-specific PF4 is an optical density (OD) is ≥0.4. True-positive PF4 results were defined as intermediate to high 4T score of ≥4, positive SRA, and clinical decision to treat for HIT. False-positive

PF4s were defined as a positive PF4 with a negative SRA, 4T score <4 (low probability), and a clinical decision to not treat for HIT as assessed by the treating clinician (hematology or vascular medicine attending). Indeterminant cases, meaning low to intermediate 4T score with a negative SRA, were classified on the basis of clinical assessment and treatment per clinical team. Descriptive statistics were used to analyze data.

3 | RESULTS

A total of 1839 patients with a PF4 result were screened, and 254 with ESRD were included for analysis (see Figure 1). The median age was 65 years, with 53% being men, and the median body mass index was 28 kg/m^2. In our population, 93 (36.6%) had documented sepsis, 20 (7.9%) were on extracorporeal membrane oxygenation (ECMO), and 54 (21.2%) underwent cardiac surgery with the use of cardiopulmonary bypass. A total of 140 (55.1%) patients were on HD, 91 (35.8%) were on CVVH, 21 (8.3%) had a CrCl < 15 mL/min without receiving RRT, and two (0.8%) were on PD. A total of 100 patients (43.3%) were receiving therapeutic UFH/LMWH, 132 (52.0%) were receiving prophylactic UFH/LMWH, and 65 (25.6%) received intraoperative heparin. Of note, 43 patients (16.9%) received a combination of therapeutic, prophylactic, or intraoperative heparin. Most patients received UFH (81.1%), followed by a combination of both LMWH and UFH (9.4%) and then LMWH only (0.4%). There were 24 patients (9.1%) who did not have documented heparin use during their hospital admission or in our health system before admission. We could not confirm whether they had exposure outside of our health system based on limited access to these electronic medical records. For these patients, a score of "0" was assigned for the heparin exposure component of the 4T score. The most common route of administration was subcutaneous (43.7%) followed by intravenous (32.5%) (see Table 1).

Of the 254 patients, 29 (11.4%) had a positive PF4. The median 4T score for PF4-positive patients was 5, whereas the median 4T score for PF4-negative patients was 3. Of note, the median score for thrombocytopenia in both PF4-positive and PF4-negative groups was 2 (platelet drop 30%-50%), yet the median thrombosis score was 0 (platelet drop <30%) in both groups (see Table 2). Of the 29 patients with a positive PF4, 10 had a positive SRA and 18 had a negative SRA. In the 10 patients with a positive SRA, the PF4 result was considered a true positive, and treatment for HIT was promptly initiated. One patient with a positive PF4 did not have an SRA collected; however, they had a high probability 4T score of 6 and a PF4 OD of 1.9. In this case, an SRA was deemed not needed by the covering team, and the patient was diagnosed with HIT and treated accordingly; we therefore classified this as confirmed HIT (PF4 result considered true positive). Of the 18 patients with a positive PF4 and negative SRA, 10 of these patients were classified as indeterminant cases with an intermediate to high 4T score of ≥4. Three of these patients were treated for HIT despite the negative SRA, whereas seven of them were not treated for HIT by the treating clinician. The remaining eight patients who had a positive PF4 but negative SRA and low probability 4T score were not diagnosed with HIT by the covering service; these patients were classified as false-positive PF4s (see Figure 1). Of the false positives, there were no patients who were treated with ECMO or who had undergone cardiopulmonary bypass.

Overall, of the 29 patients with a positive PF4, 8 (27.6%) were found to have false-positive results and were not diagnosed with HIT based on negative SRA and/or clinical assessment. The range of the PF4 values in the group defined as false positives was 0.429 to 1.28, with 1 of the 8 patients (12.5%) having an OD ≥ 1.0. Of the 18 patients who had a positive PF4 and negative SRA, OD values ranged from 0.429 to 1.574, with only 6 patients (33%) having a PF4 >1.0 and only 1 patient (5.6%) having an OD >1.5.

Of the 10 patients with a positive PF4 and positive SRA, the PF4 OD values ranged from 0.558 to 3.128. A total of 8 (80%) patients had an OD of >1.0, and 6 (60%) patients had an OD value >1.5. Of the 18 patients with a positive PF4 and negative SRA, OD values ranged from 0.429 to 1.574. A total of 6 of 18 (33%) patients with a negative SRA had an OD >1.0, and 1 (5.6%) had an OD value >1.5. Moreover, 9 of 10 (90%) patients in the positive SRA group had an intermediate to high 4T score, whereas 10 of 18 (55%) patients in the SRA-negative group had an intermediate to high 4T score (see Table 3).
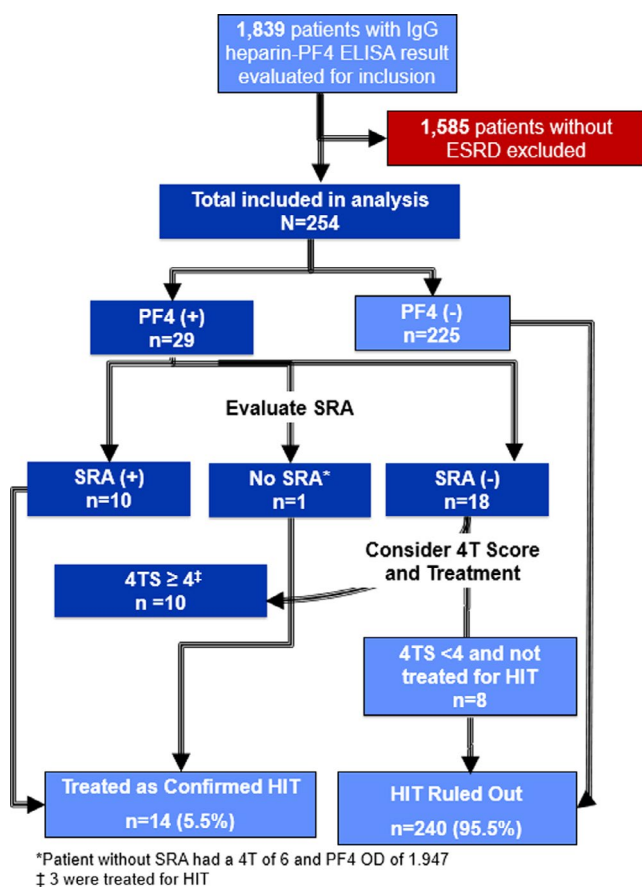

FIGURE 1 Serotonin release assay and PF4 antibody results

TABLE 1 Baseline characteristics

Characteristic	Patients (n = 254)
Age, y, median (IQR)	65 (56-73)
Male sex, n (%)	160 (63.0)
BMI, median (IQR)	28 (22.7-34.4)
ESRD subtype, n (%)	
CrCl < 15 mL/min without RRT	21 (8.3)
CVVH	91 (35.8)
Hemodialysis	140 (55.1)
Peritoneal dialysis	2 (0.8)
Indication for anticoagulant, n (%)[a]	
Therapeutic	110 (43.3)
Prophylactic	132 (52.0)
Intraoperative	65 (25.6)
Heparin exposure type, n (%)	
UFH only	206 (81.1)
LMWH only	1 (0.4)
UFH and LMWH	24 (9.4)
No heparin documented	23 (9.1)
Heparin exposure route, n (%)[b]	
Subcutaneous	101 (43.7)
Intravenous	75 (32.5)
Combination of routes	40 (17.3)
Flushes	6 (2.6)
Other	9 (3.9)
Sepsis, n (%)	93 (36.6)
ECMO, n (%)	20 (7.9)
Cardiac surgery with CPB, n (%)	54 (21.3)

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; CPB, cardiopulmonary bypass; CVVH, continuous venovenous hemofiltration; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; IQR, interquartile range; LMWH, low-molecular-weight heparin; RRT, renal replacement therapy; UFH, unfractionated heparin.

[a]Some patients had more than one indication for anticoagulant use so total percentage >100%.

[b]n = 231, as 23 patients did not have documentation of heparin.

4 | DISCUSSION

Our institution has observed an increased incidence of positive PF4 but negative SRA values specifically in patients with ESRD; thus, the aim of our study was to evaluate whether ESRD may increase the likelihood of false-positive HIT diagnoses. The incidence of false-positive PF4 antibodies can have potentially negative consequences on patient care, as it can lead to a longer length of stay for HIT evaluation and management, including inappropriate discontinuation of heparin if needed for therapeutic anticoagulation, unnecessary use of a direct thrombin inhibitor (DTI), inappropriate use of therapeutic anticoagulation in patients without another indication for anticoagulation,

TABLE 2 4T scores and associated components

	PF4 positive (n = 29)	PF4 negative (n = 225)
Thrombocytopenia point(s)	2 (1-2)	2 (1-2)
Timing point(s)	1 (1-2)	0 (0-1)
Thrombosis point(s)	0 (0-1.5)	0
Other causes point(s)	1 (0-1)	1 (0-1)
Total 4T score	5 (3-6)	3 (2-4)
Confirmed HIT, n (%)	14 (48.3)	0

Notes: All values are expressed as median (interquartile range) unless otherwise specified.
Abbreviations: HIT, heparin-induced thrombocytopenia; PF4, platelet factor 4.

or awaiting therapeutic international normalized ratio on warfarin. There are several drawbacks to using a DTI, such as lack of a specific reversal agent, cost, and inability to accurately monitor therapy in patients with abnormal baseline partial thromboplastin times. Due to the potential for a false-positive PF4 test, pretest probability and clinical judgment must be used before ordering this test. Some patients in our analysis had a PF4 sent with a 4T score of ≤3 despite the recommendations of our institutional guidelines. As stated above, both PF4-positive and -negative groups had similar rates of platelet drop and very low rates of thrombosis. This may reflect the fact that thrombocytopenia can occur in up to 55% of patients with renal dysfunction, making the diagnosis of HIT and the use of the 4T score challenging in this patient population.[4,14] We had a high proportion of patients who underwent cardiopulmonary bypass, had sepsis, and were on ECMO, all of which impact the incidence of thrombocytopenia in our patient population, driving higher 4T scores and potentially leading to the inappropriate ordering of PF4 tests.[15–17]

It is important to note that patients may develop IgG-specific PF4-heparin antibodies that do not result in any activation of platelets; therefore, a positive PF4 alone should not be the sole determinate in diagnosing HIT.[18] Our study found that patients with negative SRAs were more likely to have an OD value <1.0 and also <1.5. This suggests that we might need a different pretest probability score or consider a higher OD cutoff for patients with ESRD due to the numerous reasons for thrombocytopenia. Furthermore, alternative diagnoses should be thoroughly evaluated before sending a PF4 in this population, given the increased chance of false positives. Another study conducted at our institution by Richie et al[14] evaluated PF4 values in all patients assessed for HIT and found that OD values ≥0.8 and ≥1.0 had a higher specificity as compared to a cutoff OD of 0.4 based on corresponding SRA values. This study, involving 140 patients, identified specificity values of specificity of 61.5% versus 87.2% and 91.5% at PF4 heparin-ELISA OD values of ≥0.4, 0.8, and 1.0 OD units, respectively. While some institutions use an OD cut off of >1.0 for a positive PF4 value, our institution continues to use a conservative cutoff of 0.4 in institutional guidelines to mitigate the potential risk of missing a true HIT positive diagnosis with PF4 < 1.0.

TABLE 3 Clinical and laboratory results for suspected HIT

IgG ELISA PF4 OD, n (%)	SRA negative (n = 18)	SRA positive (n = 10)
OD 0.4-0.8	9 (50)	1 (10)
OD 0.8-1.0	3 (17)	1 (10)
OD > 1.0	6 (33)	8 (80)
4T score, n (%)	**SRA negative (n = 18)**	**SRA positive (n = 10)**
Low suspicion (≤3)	8 (44)	1 (10)
Intermediate suspicion (4–5)	6 (33)*	6 (60)
High suspicion (≥6)	4 (22)*	3 (30)
PF4 result by 4T score, n (%)	**PF4 OD 0.4–1.0 (n = 12)**	**PF4 OD > 1.0 (n = 6)**
Low suspicion (≤3)	7 (58.3)	1 (16.7)
Intermediate suspicion (4–5)	2 (16.7)	4 (66.7)
High suspicion (≥6)	3 (25.0)	1 (16.7)

Abbreviations: OD, optic diameter; PF4, platelet factor 4; SRA, serotonin release assay. *Of the 10 SRA-negative patients with intermediate-to-high suspicion for HIT, 7 were deemed to not have clinical HIT by the treating physician and 3 were deemed to potentially still have clinical HIT and were treated as such.

*Of the 10 SRA-negative patients with intermediate-to-high suspicion for HIT, 7 were deemed to not have clinical HIT by the treating physician and 3 were deemed to potentially still have clinical HIT and were treated as such.

Risk factors for an inaccurate diagnosis of HIT in ESRD are not well understood. There are few a small, observational studies examining the diagnosis of HIT in ESRD.[9,19,20] Maharaj et al[9] examined 212 outpatients receiving hemodialysis with UFH as the intracatheter anticoagulant agent over 6 years. This study used an OD of >0.4 as the cutoff for a positive PF4 and classified a "strong" immune response as having an OD ≥ 1.0 and a "weak" immune response as having an OD between 0.4 and 1.0. This study showed that while 69 (32.5%) patients developed PF4 antibodies over the 6-year period, the majority of patients with an immune response had an early peak response within 1 month of being on hemodialysis, with a waning response in immunity over 6 months despite consistent exposure to heparin. Of note, none of these patients had significant thrombocytopenia or thrombotic events. There was no discussion of collection or assessment of SRAs in this study. Overall, these authors concluded that there is a temporal pattern of PF4 antibodies in outpatients undergoing HD and that positive PF4 antibodies do not necessarily correlate with platelet activation. This study population differs from ours, as these were outpatients receiving routine hemodialysis, whereas our study includes inpatients receiving both routine and emergent HD, CVVH, or PD therapy. Furthermore, 35.8% (n = 91) of our population was on CVVH, and although there is literature describing the risk of thrombocytopenia in CVVH, there is a paucity of evidence on how to take this into account when determining the pretest probability of HIT.[18,19]

Zhao et al[21] conducted a 2-year prospective review of 661 patients receiving maintenance HD and UFH or LMWH as intracatheter hemodialysis anticoagulants. The aim of this study was to determine the positivity rate of PF4 antibodies as well as the association of positive PF4 with thromboembolic events and death. This study found a PF4 positivity rate of 5.6%, but they did not find any correlation between positive PF4 antibodies with the occurrence of clinical thromboembolic events or death. Of note, this publication did not discuss collection or assessment of SRAs. These results suggest that a positive PF4 may not be as strong a predictor for clinical HIT in patients undergoing routine hemodialysis.[21]

Our study has several limitations as a single-center, retrospective analysis. These include missing data on heparin exposure before admission in 9.1% of the population and a relatively small sample size in a complex patient population. As the diagnosis of HIT rests on both clinical interpretation and laboratory testing, both of which are subject to misclassification; this is another limitation of any analysis of patients diagnosed with HIT. In patients who did not have a documented 4T score in the chart, there is a possibility of a discrepancy between our study team's 4T calculation and the primary team's assessment. In these few instances, we used our study team's 4T score for this analysis.

We found that 4T scores and PF4 results did not consistently correlate with a clinical diagnosis of HIT in our patients with ESRD. Over 70% of the patients with intermediate to high 4T scores with a PF4 OD >1.0 and negative SRAs were not treated for HIT with an alternative anticoagulant agent after further clinical assessment. No adverse events such as thromboembolic events or death were reported.

5 | CONCLUSION

In patients with ESRD, clinical judgment is essential to make the diagnosis of HIT. The traditional diagnostic tools of 4Ts score and PF4-heparin ELISA may not be accurate in this population. Our study found that higher PF4 ODs and high-suspicion 4T probability scores did not necessarily correlate with an SRA-positive HIT diagnosis. Further investigation into the optimal strategy of HIT diagnosis in the ESRD population is warranted.

RELATIONSHIP DISCLOSURE

Dr Jean Connors is a consultant for Abbott, Anthos Therapeutics, Bristol-Myers Squibb, eXlthera, and Five Prime Therapeutics. All other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

JK led the project, contributed to the design and implementation of the research and to the analysis of the results, and was the primary writer of the manuscript. KWS conceived the project idea and contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. JR contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript. TDB contributed to data collection and editing of the manuscript, including approval of the manuscript to be published. CT contributed to data collection and editing of the manuscript, including approval of the manuscript to be published. JMC contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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