Journal of Biosciences and Medicines, 2025, 13(5), 46-58
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Incidence of Thrombocytopenia in Patients Undergoing Continuous and Prolonged Intermittent Renal Replacement Therapy

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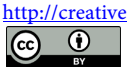
How to cite this paper: Schneider, S.L., Lathrop, C.B. and Belanger, E.R. (2025) Incidence of Thrombocytopenia in Patients Undergoing Continuous and Prolonged Intermittent Renal Replacement Therapy. *Journal of Biosciences and Medicines*, **13**, 46-58.
https://doi.org/10.4236/jbm.2025.135005

Received: April 3, 2025
Accepted: May 13, 2025
Published: May 16, 2025



Abstract

Background: Thrombocytopenia is commonly noted in critically ill patients resulting from various etiologies, including but not limited to sepsis, shock, or medications. Critically ill patients receiving renal replacement therapy (RRT) may be on concomitant heparin, raising suspicion for heparin-induced thrombocytopenia (HIT). However, literature suggests that thrombocytopenia may occur due to continuous renal replacement therapy (CRRT) itself. The primary objective of this study is to evaluate the incidence of thrombocytopenia in patients receiving both continuous renal replacement therapy and prolonged intermittent renal replacement therapy (PIRRT). **Methods:** This retrospective observational analysis aimed to evaluate thrombocytopenia in patients receiving CRRT, PIRRT, or both in a single admission. Data was gathered from patients receiving extended RRT while admitted to a single institution from November 2021 to October 2023. The primary outcome was incidence of thrombocytopenia after initiating extended RRT, as defined by a reduction in platelet count to less than 150×10^9/L in a previously nonthrombocytopenic patient. **Results:** Of the patients included in this study undergoing extended RRT, 32/51 (62.8%) experienced thrombocytopenia either during RRT or within 24 hours of RRT completion. The mean baseline platelet count was 250.7×10^9/L and the mean percent change in platelet count was a decrease of 43.5%. **Conclusion:** CRRT and PIRRT were associated with a high incidence of new onset thrombocytopenia in patients admitted to the ICU.

Keywords

Continuous Renal Replacement Therapy, Prolonged Renal Replacement Therapy, Thrombocytopenia, Tablo® Hemodialysis System

1. Introduction

Thrombocytopenia is defined as a platelet count of $<150 \times 10^9$/L, which may place patients at risk for bleeding [1]. Mild thrombocytopenia that develops in the intensive care unit (ICU) has been shown to be associated with an increased risk for major bleeding, and severe thrombocytopenia ($<50 \times 10^9$/L) puts patients at a higher risk for mortality [2]. Thrombocytopenia has been observed in the ICU with an incidence range of 10% - 60% resulting from medications, sepsis, shock, and other comorbidities [3] [4]. The true cause of thrombocytopenia in critically ill patients may be multi-factorial or remain unclear throughout a patient's clinical course. This clinical uncertainty may prompt therapy modifications in an effort to mitigate risks associated with thrombocytopenia. Depending on differential diagnoses, such modifications include (but are not limited to) removal of suspected contributory medications, utilization of alternative anticoagulants, or escalation of anticoagulant dosing.

Patients in the ICU may require renal replacement therapy (RRT) as support for renal failure, either in the form of intermittent hemodialysis (IHD), which typically runs for 4 - 6 hours, three days a week, or extended renal replacement therapy, which runs up to 24 hours continuously [5]. Extended renal replacement therapy can be administered in the form of continuous renal replacement therapy (CRRT) or prolonged intermittent renal replacement therapy (PIRRT). PIRRT is a general term for extended renal replacement modalities, comprising sustained low-efficiency dialysis (SLED), sustained low-efficiency daily dialysis (SLEDD), and extended daily hemofiltration (EDHF). CRRT and PIRRT may be run on the same hemodialysis system [6]. CRRT is run continuously every day with minimal or no interruptions, whereas PIRRT only runs for part of a given 24-hour period but is still longer than IHD. Meta-analysis of IHD, CRRT, and PIRRT in the ICU have not shown any clear advantage in short-term patient or kidney survival [7]. However, extended modalities are a viable option for those in the ICU experiencing hemodynamic instability, as the longer duration of fluid and solute removal allows for a lower ultrafiltration rate than most IHD sessions.

Our institution utilizes the Tablo® Hemodialysis System for all extended RRT modalities, administered only on ICU floors by trained critical care nurses at a 1:1 patient-to-nurse ratio. The system's simple interface, integrated disinfection safeguards, and the ability to generate dialysate from tap water allows extended RRT to be run entirely in-house, as opposed to relying on external hemodialysis technician services [8] [9].

Exposure time of the extracorporeal systems used in RRT puts the patient at significant risk of circuit thrombosis. To decrease this incidence of thrombosis, RRT is often accompanied by anticoagulation with the use of heparin or regional citrate anticoagulation (RCA) [10]. When heparin products are utilized in any patient, there is a potential risk for heparin-induced thrombocytopenia (HIT), an antibody-mediated thrombotic thrombocytopenia [11]. Due to the concern for HIT, patients who become thrombocytopenic while undergoing RRT with hepa-

rin may have anticoagulation adjusted to non-heparin agents (e.g. RCA, argatroban, bivalirudin) with or without escalation to therapeutic dosing. HIT diagnosis and therapies with non-heparin agents are associated with higher medical costs and increased length of stay [12].

The 4Ts score is used to aid in the diagnosis of HIT and direct providers to change therapy plans and collect a functional assay and serotonin release assay (SRA). There are 4 criteria: platelet reduction of >50% and a platelet nadir >20 × 10^9/L, a clear onset of 5 - 10 days after initiating a heparin product or an onset ≤ 1 day if there was heparin exposure within the last 30 days, new thrombosis or skin necrosis, and no other apparent causes of thrombocytopenia [11] [13] [14]. A patient may receive a score of 0 - 2 for each criterion for a maximum total of 8 [13]. A score ≤ 3 is low risk for HIT with American Society of Hematology (ASH) 2018 guidelines statements suggesting remaining on the current heparin regimen. Patients with a 4Ts score of 4 - 5 are intermediate risk and scores ≥ 6 are high risk. The guidelines suggest a patient with a score ≥ 4 should have all heparin products discontinued, diagnostic testing ordered, and anticoagulation changed to a non-heparin anticoagulant immediately.

A few small studies have been completed evaluating the incidence of thrombocytopenia in CRRT. Data has shown an incidence of thrombocytopenia in patients undergoing CRRT in as many as 70% of patients, much greater than the estimated incidence of HIT (0.1% - 7%) [11] [15]. Platelet reduction may occur soon after initiating CRRT, with a mean platelet reduction from baseline of approximately 47.8% after just a few days of CRRT [16]. While the exact mechanism of platelet reduction in RRT remains uncertain, proposed mechanisms include complement activation of platelets due to dialyzer membranes, or reactions to the sterilizing solution to clean the hemodialysis system and dialysate [10].

These pilot studies provide some insight into thrombocytopenia in CRRT, but these findings are not well-established, and the Tablo® Hemodialysis System has not been evaluated for incidence of thrombocytopenia in available literature. Additionally, these studies have only included RRT sessions that run continuously, and, to the authors' knowledge, the effect of a low ultrafiltration rate running over a shorter time has not been documented. This study aimed to assess the incidence of thrombocytopenia in CRRT utilizing the Tablo® Hemodialysis System, and to establish findings in patients undergoing PIRRT.

2. Methods

This retrospective, single-center, observational study was performed at Covenant Medical Center (Saginaw, MI). Data was collected from patients admitted to the medical, surgical, and cardiovascular ICUs from November 11th, 2021-October 31st, 2023. Tablo® Hemodialysis Systems were used on all patients who received extended RRT in the form of CRRT and PIRRT. Patients had to be at least 18 years old, receive a minimum of two hours of RRT for a session to be counted, and have at least one platelet level collected after starting RRT to assess trends. Exclusion

criteria included a baseline platelet count of $< 150 \times 10^9$/L to only include nonthrombocytopenic patients at baseline; those who received chemotherapy within 21 days prior to starting RRT, as this can be an alternative cause of thrombocytopenia; and those with an unknown baseline platelet count within 24 hours prior to starting RRT, as the researchers wanted an accurate baseline value upon which to base comparisons.

The primary outcome was incidence of thrombocytopenia with a platelet count less than 150×10^9/L after initiating extended RRT in a previously nonthrombocytopenic patient. This outcome was chosen to evaluate whether there is an association between extended RRT modalities and incidence of thrombocytopenia. Given the clinical significance of a percent platelet reduction of ≥50% in the 4Ts score, all patients included in the study were stratified to one of two groups for secondary analyses: percent platelet reduction of <50% or ≥50%. Once stratified, these groups were evaluated for the following exposures: hours of RRT received; number of sessions of RRT received; number of sessions needed to reach a platelet reduction of 50% or greater; hours to thrombocytopenia after initiating RRT; hours to platelet nadir after initiating RRT; HIT diagnostic testing; concomitant heparin use at current or recent encounter; and use of parenteral direct thrombin inhibitors. The mean platelet count decrease from baseline was an additional outcome that was assessed with all patients who were included in the study, not by stratification of these groups.

Baseline platelet level was defined as a platelet level collected within 24 hours prior to starting RRT. A change in platelets was defined as a percent change to nadir from baseline during RRT or within 24 hours of discontinuing RRT. For any patient who had an increase in platelets from baseline, the lowest platelet level collected during RRT was utilized to calculate the positive change from baseline. CRRT sessions were defined with the intent of running RRT continuously at initiation as an intent-to-treat analysis. PIRRT sessions were defined with the intent of the session running only part of the day in addition to scheduled time off the hemodialysis system. PIRRT sessions were only counted if they were at least 2 hours in length. To limit discrepancies, 4Ts scores were calculated by a single researcher on all patients who had HIT diagnostic testing done, including a functional assay with or without a serotonin release assay (SRA) [7].

Continuous, ordinal, and categorical baseline characteristics were analyzed using mean (with standard deviations), median (with interquartile range), and percentage respectively. The Pearson chi-square test was used for categorical variables. An unpaired T-test was used to assess the statistical significance when comparing continuous data. Differences were considered statistically significant at a p-value of < 0.05. No adjustments were made to control for confounding variables.

Data was collected by a single researcher with access to an electronic health record (EHR) and hemodialysis system data. Hours of RRT completed were collected using records of nursing documentation of start and stop times in the EHR and hemodialysis system online database. Based on the sample size used by Ferreria and

Johnson, it was decided to collect a sample of at least 50 patients [16]. All patient records were de-identified and assigned a randomly generated identification code, in order to protect patient health information. A separate, password-protected spreadsheet was maintained linking each identification code to patient medical record numbers. Data collection stopped after the first 51 patients met inclusion criteria. Unexpected downtimes where the nurse documented the system being stopped temporarily due to patient intolerance of RRT or the hemodialysis system needing bedside maintenance were not included in the total hours on RRT. Data was compiled and statistics were calculated using MS Excel.

3. Outcomes

3.1. Baseline Characteristics

A total of 138 patients were screened with 51 meeting inclusion criteria and 87 patients being excluded. Patients were excluded based upon the following criteria: 64 had baseline platelets less than 150×10^9/L at the start of RRT; 10 did not meet the minimum requirement of two hours of RRT; 9 had RRT ordered but never started; 2 did not have at least one platelet level collected after initiating RRT due to death; and 2 were admitted outside the defined data collection time frame.

The average overall age was 65.27 [±12.35] years, with the average age similar between the two groups of <50% platelet reduction from baseline and ≥50% platelet reduction from baseline. Mean baseline platelets (10^9/L) prior to starting RRT overall was 218 [180.5 - 292] and was also similar between the two platelet groups. Most patients included were Caucasian males (**Table 1**).

There were 6 patients who received only CRRT sessions, 37 who received only PIRRT sessions, and 8 who received a combination of at least one CRRT session with at least one PIRRT session. 51% (26/51) of patients had a platelet reduction of 50% or greater from baseline overall. The mean duration of RRT sessions in all RRT patients with a platelet reduction <50% was 16 [10 - 25] hours, and those with a ≥ 50% reduction had a mean duration of RRT of 32 [24 - 66] hours. A discernable factor in having a platelet reduction of ≥50% was the total duration of RRT sessions, which showed statistical significance with a p-value of 0.02. Patients who received only PIRRT also showed statistical significance for total duration of sessions with a p-value of 0.02. Total duration of PIRRT sessions was greater in the ≥50% group (27.4 [±13.1] hours) than it was in the <50% group (17.1 [±11.5] hours). The total duration of CRRT sessions was similar between the groups with an average of 45.5 hours in the < 50% group and 48 hours in the ≥50% group. Of those who received a combination of CRRT and PIRRT, there was 1 patient with a < 50% reduction in platelets with a total RRT duration of 40 hours, and the ≥50% group had an average of 157.7 [±96.2] hours.

3.2. Outcomes

The primary outcome of thrombocytopenia onset after starting RRT occurred in 62.8% (32/51) of patients (**Table 2**). The mean platelet reduction from baseline

was 43.5%. Of those who had a platelet reduction of 50% or greater, the number of RRT sessions needed to reach a threshold of a 50% was 1 [1 - 2; 1 - 5] session. Hours to thrombocytopenia onset was similar between the platelet groups, 15 hours for the <50% group and 16 hours for the ≥50% group. However, hours to platelet nadir were greater in the ≥50% group (69 hours) than the <50% group (31 hours), suggesting a greater platelet reduction from baseline with longer RRT therapy.

Table 1. Baseline characteristics.

	Total (n = 51)	**<50% platelet reduction** (n = 25)	**≥50% platelet reduction** (n = 26)	**P-value**
Baseline platelets [median (IQR)]	218 (180.5 - 292)	209 (181 - 269)	246.5 (182.5 - 327)	----
Age [mean (SD)]	65.27 (12.35)	66.36 (13.17)	64.23 (11.76)	----
Race [%]				0.86
Black/African American [n, %]	14, 27.45%	8, 57.14%	6, 42.86%	----
Hispanic [n, %]	2, 3.92%	1, 50%	1, 50%	----
White/Caucasian [n, %]	35, 68.63%	17, 48.57%	18, 51.43%	----
Gender [%]				0.45
Male [n, %]	32, 62.75%	15, 46.88%	17, 53.13%	----
Female [n, %]	19, 37.25%	11, 57.89%	8, 42.11%	----
All RRT [n]	51	25	26	----
Total duration of sessions (hours) [median (IQR)]	24 (12 - 46)	16 (10 - 25)	32 (24 - 66)	0.02
CRRT Only [n]	6	4	2	----
Number of sessions [median]	2	2	2	----
Total duration of sessions [mean]	46.33	45.5	48	----
PIRRT Only [n]	37	20	17	----
Number of sessions [median (IQR; Range)]	2 (1 - 3; 1 - 5)	1 (1 - 2.5; 1 - 5)	3 (2 - 4; 1 - 5)	----
Total duration of sessions [mean (SD)]	21.84 (13.17)	17.1 (11.54)	27.4 (13.07)	0.02
CRRT and PIRRT [n]	8	1	7	----
Number of sessions [median]	9	4	9	----
Total duration of sessions [mean (SD)]	148 (93.16)	40	157.7 (96.15)	----

Table 2. Thrombocytopenia outcomes.

	Thrombocytopenic (n = 32)	**Nonthrombocytopenic** (n = 19)
All RRT (n = 51)	62.75%	37.25%
CRRT (n = 6)	50%	50%
PIRRT (n = 37)	62.16%	37.84%
CRRT + PIRRT (n = 8)	75%	25%
# of TABLO sessions needed to reach a 50% reduction in platelets [median (IQR; Range)]	1 (1 - 2; 1 - 5)	--
Mean platelet decrease from baseline [%]	43.49%	

There were 7 patients who went through diagnostic testing for potential HIT (Table 3). Five patients had a 4Ts score ≤ 3, indicating low probability for HIT and would not have met the ASH guideline criteria for HIT diagnostic testing [4]. One patient had a positive SRA and had the highest 4Ts score of 6 (high probability). The second highest score was a 4 (intermediate probability) [7].

Table 3. HIT Outcomes.

	Total (n = 51)	<50% platelet reduction (n = 25)	≥50% platelet reduction (n = 26)
Hours to thrombocytopenia [median]	15.5	15	16
Hours to platelet nadir [median]	44.5	31	69
Heparin product started before RRT [n, %]	40, 78.43%	20, 80%	20, 76.92%
HIT workups [n]	7	0	7
HIT positive SRA [n]	1	0	1
4Ts score ≤ 3 [n, %]	5, 71.4%	0	5
4Ts score ≥ 4 [n, %]	2, 28.6%	0	2
Anticoagulant changes in thrombocytopenic patients [n]	3	0	3
Bivalirudin [n]	1	0	1
Argatroban [n]	2	0	2

4. Discussion

Results from prior CRRT studies were repeated in this study's primary and secondary outcomes. Wester *et al.* found an incidence of thrombocytopenia in their CRRT population to be 70%, while our study found a similar incidence in extended RRT of 62.8% [15]. Notably, the PIRRT Only group also showed an incidence of 62.2%, a finding consistent with the incidence of thrombocytopenia in extended RRT as a whole. Additionally, Ferreria and Johnson found a decrease in platelets from baseline in their CRRT population to be 47.8%, while our study found a similar decrease from baseline of 43.5% in the total population [16]. The incidence of thrombocytopenia in the general ICU population has been estimated to be anywhere from 10% - 60% by various sources. When considered alongside this previous literature, the results of our study suggest that patients undergoing PIRRT or any combination of extended RRT modalities may be a high-risk group for thrombocytopenia within the general ICU population. However, controlled studies evaluating extended RRT modalities in various hemodialysis systems would have to be completed to confirm these results.

When the study population was stratified by degree of platelet reduction (<50% from baseline and ≥50% from baseline), a statistically significant difference was observed in mean RRT duration (hours). The mean RRT duration (hours) was greater in the ≥50% platelet reduction group, a trend observed across all extended RRT modalities utilized (CRRT, PIRRT, CRRT + PIRRT). This finding suggests

that longer durations of RRT with Tablo® Hemodialysis System result in a greater reduction of platelet count. Statistical significance was not analyzed on those who received CRRT alone and in those who received CRRT and PIRRT, due to the small sample size in these subgroups. However, it is worth noting that out of the patients who received both CRRT and PIRRT, the only patient who showed a platelet reduction <50% underwent a much shorter RRT duration of 40 hours, while the other 7 patients who had a ≥50% platelet reduction had an average duration of 157.7 [±96.15] hours.

No difference was observed between the platelet reduction groups when comparing time to thrombocytopenia (platelets $<150 \times 10^9$/L) after initiating RRT. However, time to platelet nadir was greater in the ≥50% reduction group. From this, the authors conclude that platelet reduction continues throughout the duration of RRT treatment, as opposed to solely an initial drop early in RRT. This finding reflects the studies done by Droege *et al.*, and Wu *et al.*, which evaluated platelet reduction in patients undergoing CRRT over 5 days and 3 days, respectively [3] [17]. A statistically significant drop in platelets was seen on each subsequent day that patients were on CRRT in Droege *et al.*, and statistical significance was seen in platelet count when compared to baseline starting on day 2 of CRRT in Wu *et al.*

The results also indicate that platelet reduction can occur quickly after initiating RRT. The average time to reach the first thrombocytopenic lab result after initiating RRT was 15.5 hours. In those who had a platelet reduction of ≥50%, the median number of sessions needed to reach the threshold of 50% was just one session. This indicates that any exposure to the extracorporeal system can result in a rapid platelet reduction.

This pilot study is the first that the authors are aware of to assess platelet reduction associated with PIRRT. Prior studies have only included patients undergoing CRRT, which allows for continuous filtration of the blood without the longer interruptions that are seen in PIRRT. The inclusion of PIRRT seemed to result in similar outcomes to those who only received CRRT in prior studies [15] [16]. Previous literature showed that continuous exposure to an extracorporeal system could result in a significant platelet reduction, but the results of this study suggest that any extended exposure to the extracorporeal Tablo® Hemodialysis System may result in a significant reduction in platelets.

These findings are consequential to the critically ill population because, currently, the only published guidelines on thrombocytopenia management in those with renal injury or disease appear in the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury guidelines, and only provide recommendations on management of suspected HIT [18]. KDIGO does not provide guidance on any other potential contributors to thrombocytopenia such as renal replacement therapy. When using the 4Ts score to assess the likelihood of HIT, the time to thrombocytopenia onset, percent reduction of platelets, occurrence of thrombosis, and presence of other potential thrombocytopenia causes are evalu-

ated. A patient with extremely high likelihood of HIT would receive a score of 2 for each criterion based on the following workup: a platelet reduction of >50% and a platelet nadir > 20 × 10^9/L; a clear onset of 5 - 10 days after initiating a heparin product or an onset ≤ 1 day if there was heparin exposure within the last 30 days; new thrombosis or skin necrosis; and no other apparent causes of thrombocytopenia. With the observed association between extended RRT and onset of thrombocytopenia, this study brings to light an additional potential cause that may be considered when scoring the fourth criterion of the 4Ts score. Thus, if a patient received otherwise modest scores on the other criteria, scoring the final criterion as 0 or 1 due to the presence of extended RRT as potential alternative cause may change the clinical evaluation for likelihood of HIT.

The data gathered in this study was specifically stratified into groups of platelet reduction of <50% or ≥50% in order to provide comparable data points that would be assessed with a 4Ts score, and the data shows that a patient initiated on an extended RRT modality in the ICU can mimic HIT onset. In the entire population, the average hours to the first thrombocytopenic level after initiating RRT was 15.5 hours. Those who did become thrombocytopenic with a reduction of ≥50% met that value after a median of just 1 RRT session. Based on this, consider a hypothetical patient admitted to the ICU, given a heparin product, started on extended RRT 5 - 10 days after admission, and then experiencing sudden platelet drop of 50% or greater within 24 hours after starting RRT. This situation would give a patient a score of 2 for onset within 5 - 10 days, and a score of 2 for a fall >50%, and would already give an intermediate 4Ts score constituting HIT diagnostic testing without looking at the other two criteria. Ruling out all other possible causes of thrombocytopenia would then yield another score of 2, giving a patient a high 4Ts score and high likelihood for HIT. The authors propose that this study provides another potential reason for thrombocytopenia to occur, meaning a patient on extended RRT with the Tablo® Hemodialysis System may receive a score of 0 for other definite causes in the last criterion of the 4Ts score. Therefore, if the findings of previous literature and this study are applied, this patient may instead be evaluated at intermediate risk for HIT, leading to a potential change in the treatment course a clinician chooses to pursue.

Our study excluded patients that had a baseline platelet count <150 × 10^9/L due to this value being recognized for a risk for complications, such as major bleeds and need for blood transfusions, by the CHEST guidelines. Prior studies on the incidence of thrombocytopenia in CRRT have designed the exclusion criteria in such a way that patients with baseline platelets <150 × 10^9/L have been included. The authors believe it is a strength that patients were only included if they did not have clinically and statistically significant risk of complications related to thrombocytopenia prior to starting RRT. Our study is partially modeled after Ferreria and Johnson, who stratified their population by groups of platelet reduction of >50% and <50%, but only excluded patients with baseline platelets of <50 × 10^9/L. The percent of those with a platelet reduction ≥50% is nearly identical, despite our

study requiring a much greater absolute platelet drop from baseline to meet that percentage value. To the authors' knowledge, it is only study to report the incidence of thrombocytopenia without including patients that some clinicians would consider to be thrombocytopenic at baseline.

Another strength includes the apparent homogeneity with previous studies and repeatable results. The incidence of thrombocytopenia and secondary outcomes, such as percent reduction from baseline and incidence of platelet reduction ≥ 50%, were consistent with existing literature. Regarding design, this study shares many features with previous investigations of thrombocytopenia in extended RRT: similar primary and secondary outcomes, critically ill population, sample size, and one-group observational design [3] [15]-[17]. This opens the opportunity for future meta-analyses to improve the generalizability and strength of findings.

The authors conclude several limitations to this study. The primary outcome was an observational assessment of incidence without a matched control group of patients not receiving RRT. Due to this design, alternative causes of thrombocytopenia cannot entirely be ruled out. Given that patients included in this study were in critical condition, there could be a number of reasons for a patient to have sudden onset of thrombocytopenia. Having additional exclusion criteria for disease states associated with a high incidence of thrombocytopenia, such as cirrhosis, may have helped study by reducing confounding variables, and this should be considered in future studies.

Individual RRT settings for each patient, such as ultrafiltration, hemodialysis, and sequential dialysis techniques were not recorded. Choice of dialyzer, dialysate flow rate, and net fluid removal, were also not collected. These parameters may have contributed to degree platelet reduction, prompting potential opportunity for further study. Individual evaluation of these dialysis parameters could also provide useful insight on the mechanisms of thrombocytopenia in RRT.

Additionally, only 51 patients were retrospectively reviewed from a single institution and with a single hemodialysis system. Due to a lack of a control group with this small cohort study, and limited available research in previous studies, we were unable to appropriately determine power for this investigation. For this reason, the conclusions of this study should purely serve as hypothesis-generating findings and incite more expansive research.

The Tablo® Hemodialysis System is not ubiquitously utilized across all institutions. Therefore, a multicenter study evaluating incidence of thrombocytopenia across multiple hemodialysis systems with a larger patient population would aid in the external validity and application of these findings.

The 4th criterion of the 4Ts score is a partially subjective measure, requiring the assessor to determine either definite or potential alternative causes of thrombocytopenia. The 4Ts scores collected in this study were assessed by a single researcher, therefore, subjective evaluation may have resulted in scoring that differs slightly from that of other clinicians. However, this method of assessment also ensured

scoring remained consistent between every patient assessed.

5. Conclusions

This study demonstrated a high incidence of new onset thrombocytopenia (62.8%) in all modalities of extended RRT, including those on CRRT, PIRRT, and a combination of CRRT and PIRRT. It is the first study to evaluate the shorter extracorporeal exposure time seen with PIRRT, and the primary outcome of incidence of thrombocytopenia was found to be nearly identical between the CRRT and PIRRT populations. The incidence of thrombocytopenia in every extended RRT modality group evaluated reflects prior studies that have only included CRRT. Time to thrombocytopenia onset (platelet $<150 \times 10^9$/L) was very rapid after initiating any extended RRT modality, with the mean hours to thrombocytopenia being just 15.5 hours. The inclusion of PIRRT in this study evaluating outcomes such as time to thrombocytopenia onset and incidence of thrombocytopenia, suggests that any exposure to the extracorporeal system results in a rapid drop in platelets.

Total duration of RRT was evaluated in stratified groups of patients with ≥50% platelet reduction from baseline and <50% reduction from baseline. It was found that the total duration (hours) of RRT received was greater in the ≥50% group. Time to platelet nadir was also greater in the ≥50% group. These outcomes indicate that longer durations of RRT resulted in a greater reduction of platelets from baseline with each subsequent session of extended RRT.

There were 7 patients who received diagnostic testing for heparin-induced thrombocytopenia (HIT) as a result of a sudden platelet reduction. Only one patient had a positive SRA, indicating HIT. This patient received the highest 4Ts score (6) of the 7 patients who were tested.

Results of this study and previous literature associate extended RRT modalities with incidence of thrombocytopenia. Thus, a score of 1 or 0 may be considered for the 4th criterion of the 4T score in patients receiving CRRT or PIRRT. Recognition of the association between extended RRT and thrombocytopenia further refines the assessment of HIT likelihood, aiding in differential diagnosis and subsequent management of thrombocytopenia in the ICU population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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