Published in final edited form as:

Crit Care Med. 2019 April ; 47(4): e325–e331. doi:10.1097/CCM.0000000000003598.

Effects of Baseline Thrombocytopenia and Platelet Decrease Following RRT Initiation in Patients with Severe AKI

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Abstract

Objectives: Thrombocytopenia is common in critically ill patients with severe acute kidney injury and may be worsened by the use of renal replacement therapy. In this study, we evaluate the effects of renal replacement therapy on subsequent platelet values, the prognostic significance of a decrease in platelets, and potential risk factors for platelet decreases.

Design: Post hoc analysis of the Acute Renal Failure Trial Network Study.

Setting: The Acute Renal Failure Trial Network study was a multicenter, prospective, randomized, parallel-group trial of two strategies for renal replacement therapy in critically ill patients with acute kidney injury conducted between November 2003 and July 2007 at 27 Veterans Affairs and university-affiliated medical centers.

Subjects: The Acute Renal Failure Trial Network study evaluated 1,124 patients with severe acute kidney injury requiring renal replacement therapy.

Interventions: Predictor variables were thrombocytopenia at initiation of renal replacement therapy and platelet decrease following renal replacement therapy initiation.

Measurements and Main Results: Outcomes were mortality at 28 days, 60 days, and 1 year, renal recovery, renal replacement therapy free days, ICU-free days, and hospital-free days. Baseline thrombocytopenia in patients requiring renal replacement therapy was associated with increased mortality and was also associated with lower rates of renal recovery. A decrease in platelet values following renal replacement therapy initiation was associated with increased mortality. Continuous renal replacement therapy was not an independent predictor of worsening thrombocytopenia compared with those treated with intermittent hemodialysis.

Conclusions: Baseline thrombocytopenia and platelet decrease following renal replacement therapy initiation were associated with increased mortality, and baseline thrombocytopenia was associated with decreased rates of renal recovery. Continuous renal replacement therapy did not decrease platelets compared with hemodialysis.

Keywords

Thrombocytopenia; Acute Kidney Injury; Renal Replacement Therapy

BACKGROUND

Thrombocytopenia is common in critically ill patients in the ICU with prevalence rates ranging from 15% to 55% (^{1–16}). ICU thrombocytopenia is independently associated with increased mortality, and the mortality rate is proportional to thrombocytopenia severity (^{1,3,4,7–20}). Risk factors for thrombocytopenia include sepsis, liver dysfunction, central line placement, acute kidney injury (AKI), prolonged ICU stay, vasopressor support, and severity of multiple organ failure (^{4,6,7,10,11,15,16,21–24}). Critically ill patients frequently have more than one risk factor, making an exact cause of thrombocytopenia difficult to identify.

Thrombocytopenia may mediate poor patient outcomes via multiple mechanisms. For example, platelets may contribute directly to organ failure through microvascular dysfunction caused by activated platelet aggregation (²⁵) or in response to endothelial damage (²⁶). Data also suggest that platelets play an important role in host immune responses by mediating recruitment and translocation of mononuclear cells and lymphocytes into areas of inflammation (^{27,28}). Finally, platelets can contribute to the inflammatory response through release of cytokines and other molecular mediators (²⁹).

Rates of thrombocytopenia in critically ill patients with severe AKI requiring renal replacement therapy (RRT) are even higher than in the general ICU population, and thrombocytopenia independently predicts mortality in RRT patients (^{2,30–33}). Limited data suggest that RRT itself may further decrease platelet values through platelet activation secondary to contact with dialysis membranes (^{34,35}); however, it remains unclear whether RRT contributes to a reduction in platelets, or whether a reduction in platelets following RRT initiation is associated with increased mortality.

We hypothesized that both baseline thrombocytopenia and decrease in platelets following RRT initiation would predict higher rates of mortality. Considering that blood-membrane contact is longer in continuous RRT (CRRT) than hemodialysis, we also hypothesized that CRRT would be independently associated with platelet loss compared to hemodialysis. We sought to evaluate our hypotheses in a post hoc analysis of data from the Acute Renal Failure Trial Network (ATN) study.

METHODS

Study Population:

The ATN study was a multicenter, randomized, controlled trial evaluating conventional versus intensive dosing of RRT in critically ill patients with AKI (^{36,37}). Briefly, 1,124

patients with AKI and sepsis or failure of at least one nonrenal organ were randomized to conventional or intensive RRT. Patients converted between modalities of RRT based on hemodynamic stability. In the intensive arm, CRRT effluent flow rate was 35 mL/kg per hour, and hemodialysis and slow low-efficiency dialysis (SLED) were provided six times per week at a prescribed Kt/V_{urea} of 1.2–1.4 per session; in the conventional arm, CRRT effluent flow rate was 20 mL/kg per hour, and hemodialysis and SLED were provided three times per week. Results were published in 2008, and there were no differences in outcomes.

After obtaining local institutional review board approval, we received the study dataset from the National Institute of Diabetes and Digestive and Kidney Diseases central repository. Patients who died within 48 hours of treatment initiation were excluded.

Predictors:

Baseline platelet values were divided into categories of normal ($> 100 \times 10^3/\mu\text{L}$) and low ($< 100 \times 10^3/\mu\text{L}$). A cut-off of $150 \times 10^3/\mu\text{L}$ was not used because too few patients had baseline platelets above this value. Changes in platelets after RRT initiation were divided into categories of platelet increase or platelet decrease.

Outcomes:

The primary outcome was 60-day mortality. Secondary outcomes were 28-day mortality, 1-year mortality, renal recovery, defined in survivors as being free of dialysis by day 28, RRT-free days out of 28 days, ICU-free days out of 60 days, and hospital-free days out of 60 days.

Other Variables:

Covariates in the fully adjusted model included age, race, gender, body mass index, albumin, modified Sequential Organ Failure Assessment (mSOFA) score at admission and at 72 hours (mSOFA excluded the coagulation component), and the Charlson comorbidity score. Variables evaluated for an association with platelet decrease included the cause of AKI, defined as sepsis-induced, postsurgical, malignancy-related, and/or liver injury-induced, RRT modality, categorized as intermittent hemodialysis or CRRT, blood flow rate (BFR), and anticoagulation type, categorized as none, heparin, citrate, or other.

Statistical Analysis:

Mean $\pm$ SD or counts and percentages were used to describe the distribution of continuous and categorical variables, respectively. Analysis of variance, Kruskal Wallis, or chi-square tests were used as appropriate.

To minimize risk of bias caused by missing data, we performed multiple imputation to impute missing values. Multivariable regression analyses were performed on all patients following multiple imputation and were repeated after restricting to patients with complete covariate data. Table S1 outlines the numbers of subjects affected by missing data.

Finally, we attempted to determine risk factors for platelet decrease following RRT initiation. For this analysis, patients initiated on SLED were excluded. Univariate regression

was performed with the variables outlined above. All variables found to be significant in univariate modeling to a significance level of p value of less than 0.1 were included in the multivariable model.

RESULTS

Associations of Baseline Platelet Values at the Time of RRT Initiation

Baseline: One-thousand one-hundred twenty-four patients from the ATN trial were included in the analysis. In the ATN study, the mean delivered Kt/V_{urea} was 1.32. The mean prescribed dose of continuous venovenous hemodiafiltration (CVVHDF) was 36.2 ± 3.8 mL/kg/hr in the intensive group and 21.5 ± 4.3 in the conventional group. In the first 48 hours following randomization, the average hemodialysis treatment was 4.0 hours, and the average CVVHDF treatment was 21.0 hours. Heparin anticoagulation was used in 30% of hemodialysis treatments, and no anticoagulation was used in 66% of treatments. For CVVHDF, no anticoagulation was used in 57% of treatments, heparin in 20% of treatments, and citrate in 19% of treatments. The remaining circuits used “other” anticoagulation, which was most often Argatroban. Average BFR was 360 mL/min in hemodialysis treatments and 145 mL/min in CVVHDF treatments (³⁷). A total of 544 patients (48%) had platelets less than $100 \times 10^3/\mu\text{L}$ at the initiation of RRT, and 200 (18%) had severe thrombocytopenia with a value less than $50 \times 10^3/\mu\text{L}$ at initiation. Patient characteristics are given in Table 1.

Outcomes: Thrombocytopenia at baseline was highly associated with 28-day mortality, 60-day mortality, and 1-year mortality even after adjustment for confounding factors. Patients with thrombocytopenia were 44% less likely to recover renal function and consequently were likely to have fewer RRT-free days. There were trends toward fewer ICU-free days and fewer hospital-free days which did not reach statistical significance (Table 2). Restricting the analysis to the 827 patients with complete data did not meaningfully impact the results (data not shown).

Associations of Platelet Decrease Following RRT Initiation

A total of 989 patients (87.9%) survived for 48 hours following RRT initiation. Of those, 619 patients (63%) had a decrease in platelets following RRT initiation, with an average decrease of 33%. A total of 139 patients (14%) had a decrease in platelets of at least 50% from baseline.

Decreased platelets from baseline following RRT initiation significantly associated with increased 60-day mortality in multivariable analysis. There were trends toward increased 28-day and 1-year mortality that did not reach statistical significance. Lack of renal recovery was not associated with a platelet decrease, and there were no differences in RRT-free days or ICU-free days. When mSOFA scores at 72 hours were used instead of baseline mSOFA scores at baseline, there were no differences in outcomes observed (Table 3).

Results in Patients With Normal Platelet Values at RRT Initiation

In the 580 patients (52%) with platelets greater than $100 \times 10^3/\mu\text{L}$ at initiation of RRT, 517 (89%) survived at least 48 hours. Of those, 346 (67%) experienced a decrease in platelets with an average decrease of 30%.

After the full model adjustment using baseline mSOFA scores, a decrease in platelets from a normal baseline following RRT initiation was significantly associated with increased 60-day mortality. There were again trends toward increased 28-day and 1-year mortality that did not reach statistical significance. Notably, within this group a decrease in platelets predicted a lack of renal recovery that was statistically significant. When mSOFA scores at 72 hours were used instead of mSOFA scores at baseline, ICU-free days became statistically significant, and renal recovery became insignificant with a p value of 0.059 (Table 4).

Results in Patients Initiated on Hemodialysis

A total of 285 patients were either initiated on hemodialysis or transitioned to hemodialysis within 48 hours. Of these, 137 were randomized to the conventional group and 147 to the intensive group, and 62 patients (45%) and 69 patients (47%), respectively, had a decrease in platelets. Among these patients, the average platelet decreases were 21% and 25%, respectively, which did not reach statistical significance ($p = 0.2$) (data not shown).

Predictors of Decreased Platelets Following RRT Initiation

In univariate analysis, modality of RRT on day 1, modality of RRT on day 2, AKI due to liver disease, mSOFA, baseline platelets, and total diafilters lost were found to have p value of less than 0.1. In the final multivariable regression, there was no statistical difference in rates of platelet decrease in subjects started on CRRT as opposed to hemodialysis. Results of the univariate regression are shown in Table S2, and the final multivariable model is shown in Table 5.

DISCUSSION

This study is one of the largest to date evaluating the effects of thrombocytopenia and subsequent platelet decrease in critically ill patients with severe AKI initiated on RRT. Our results show that platelet decrease is common in patients undergoing RRT with a prevalence of greater than 50% and that thrombocytopenia is associated with increased mortality even after statistical adjustments for potentially confounding variables. A decrease in platelets following RRT initiation was associated with increased 60-day mortality. CRRT was not associated with a reduction in platelets compared with hemodialysis. We also found that thrombocytopenia at RRT initiation and a platelet drop in patients with normal platelets prior to RRT initiation predicted decreased rates of renal recovery.

Our findings are consistent with two previous studies that evaluated thrombocytopenia in patients undergoing CRRT. A study evaluating 541 patients showed that platelet count prior to initiation of CRRT was a strong predictor of mortality. Although platelet decreases following CRRT initiation were not directly evaluated, the authors further found that in patients who had a normal platelet count of greater than $150,000 \times 10^9$ at CRRT initiation, a

decrease to less than $50,000 \times 10^9$ platelets was associated with higher mortality (³²). Another retrospective study evaluated 125 patients who received CRRT for more than 72 hours (³³) and reported that a platelet decline of greater than 20% was associated with higher mortality rates. However, thrombocytopenia at CRRT initiation was not associated with mortality.

A major question raised by this analysis is whether thrombocytopenia is simply a marker of illness severity or a direct contributor to mortality that could be a target for future intervention. To further evaluate the possibility that our results were due to worsening underlying illness, we adjusted the statistical analyses using admission mSOFA values and mSOFA values at 72 hours (or at 48 hr if the patient died between 48 and 72 hr). Worsening of serial Sequential Organ Failure Assessment (SOFA) scores has been shown to correlate with increased mortality (³⁸), likely as a reflection of worsening illness. The statistical associations did not change significantly, suggesting that a platelet decrease predicts mortality independent of changes in the other SOFA components.

More recently, investigators have shown that platelets have many roles beyond thrombus formation. Platelets mediate the recruitment of leukocytes and facilitate their translocation to areas of inflammation (^{27,28}). Platelets also release cytokines and other molecular mediators such as serotonin, epinephrine, norepinephrine, nitric oxide, and vascular endothelial growth factor, contributing directly to the inflammatory response in the critically ill (²⁹). Based on these data, it is plausible that thrombocytopenia in the critically ill is a marker of platelet dysregulation which can directly contribute to increased morbidity and mortality. Further research into the role of thrombocytopenia in critical illness is needed.

Another question raised by this analysis is whether RRT directly contributes to platelet decreases, and if so, by what mechanism. Although the effects of contact between blood and synthetic membranes have not been well studied in CRRT, they have been evaluated in other extracorporeal treatments. During cardiopulmonary bypass, contact between blood and the oxygenator membrane has been shown to cause activation of platelets. These platelets are thought to then be consumed peripherally, resulting in a significant decrease in platelet levels (³⁹). Platelet exposure to dialysis membranes has also been shown in the hemodialysis population to increase rates of platelet activation (³⁴). In CRRT, results of studies evaluating platelet activation have been mixed. In a study of eight patients treated with continuous venovenous hemofiltration, mass spectroscopy was used to measure GP53 and P-selectin, markers of platelet activation, and did not observe a difference when comparing prefilter with postfilter levels (⁴⁰). However, another study measured platelet levels before and after the CRRT filter and estimated that 625×10^9 platelets were lost across the diafilter daily (³⁵). Further research into the platelet effects of blood-membrane contact is needed.

Our study is the first to compare modalities of RRT and their association with platelet decrease. We found that CRRT, compared with hemodialysis, was associated with platelet decreases in the univariate analysis. However, this result was attenuated by incorporation of illness severity, liver disease, and filter loss into the final model. These data suggest that CRRT, relative to hemodialysis, does not independently contribute to platelet loss. This suggests that contact time beyond 4 hours does not significantly increase platelet loss,

perhaps due to protein coating of the membrane surface. Additionally, platelet activation may be a rapid phenomenon. In cardiopulmonary bypass, platelet activation markers are upregulated as soon as 5 minutes after initiation and peak at 120 minutes (⁴¹). Our finding is further supported by our comparison of rates of platelet decrease in the conventional and intensive groups in patients initiated on hemodialysis only. The intensive hemodialysis group had twice as much filter exposure as the conventional hemodialysis group, without the confounding factors involved in comparing hemodialysis with CVVHDF. Although the percentage of platelet loss was higher in the intensive group, this did not achieve statistical significance.

Of note, the type of anticoagulation used during RRT did not correlate with the development of thrombocytopenia, nor did the anticoagulation type impact rates of bleeding (data not shown). Kidney Disease Improving Global Outcomes (KDIGO) recommends the use of citrate (⁴²), and the use of anticoagulation has been shown to increase circuit life (⁴³); however, use of anticoagulation is not universal. The variety of anticoagulation regimens used in the ATN study reflects the variety in current practice patterns. In our study, filter loss was associated with thrombocytopenia on univariate analysis. It is possible that platelet activation predisposes to filter loss, which may worsen outcomes by causing blood loss and decreased clearance (⁴⁴). However, we were unable to examine this in our current analysis. The effects of anticoagulation on platelet counts and platelet function in RRT warrant further investigation.

One final point is the observation that both thrombocytopenia prior to RRT initiation as well as platelet decreases in patients without thrombocytopenia at baseline predicted a lack of renal recovery. To our knowledge, this relationship has not been previously reported. This association may be due to increased rates of microthrombi formation, reflected by thrombocytopenia, causing microvascular flow abnormalities (²⁵). Thrombocytopenia may also reflect severe endothelial injury leading to platelet consumption (²⁶). This finding needs to be replicated in other studies, but if confirmed could be useful in predicting the likelihood of renal recovery in critically ill patients.

Our study has several strengths including the large ATN database used for analysis, the availability of a large number of covariates for adjustment, and the high utilization of both RRT modalities (hemodialysis and CRRT), as well as several notable limitations. First, we cannot exclude the possibility of residual confounding despite our use of multivariable analysis. We were unable to evaluate for the presence of diffuse intravascular coagulation and heparin-induced thrombocytopenia, for instance. Adjustments for SOFA score may not have fully addressed the differences between patients initiated on CVVHDF who were more hemodynamically unstable than those initiated on hemodialysis. The ATN study was designed to allow for rapid changes in modality as deemed appropriate by treating services, which introduced some heterogeneity into the treatment regimens. Finally, as noted in the discussion, we were unable to assess the mechanism of platelet decrease following RRT initiation.

CONCLUSIONS

Our study demonstrates that thrombocytopenia has important prognostic implications for mortality and renal recovery in critically ill patients started on RRT and that even a mild decrease in platelet counts following RRT initiation predicts mortality independent of underlying disease severity. Additionally, our data indicate that the platelet decrease is independent of RRT modality and type of anticoagulation. Future work should explore the potential pathophysiologic link between RRT and platelet dysfunction.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank all the patients who participated in the ATN study as well as the investigators and study nurses who contributed to data collection and analysis in the ATN study. We also thank the National Institute of Diabetes and Digestive and Kidney Disease for project approval and access to the ATN dataset.

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Table 1.

Baseline characteristics of the two groups based on platelet count prior to RRT initiation.

Variables (baseline)		Platelets > 100,000 x10 ³ /μL N = 580	Platelets < 100,000 x10 ³ /μL N = 544	p-value
Age		60.2 ± 15.1	59.1 ± 15.3	0.2
Gender	Male	433 (75%)	361 (66%)	<0.001
	Female	147 (25%)	183 (34%)	
Caucasian Race		425 (73%)	391 (72%)	0.7
Modified SOFA Score		12.0 ± 3.6	13.2 ± 3.3	<0.001
Body Mass Index (kg/m ²)		28.6 ± 6.3	27.8 ± 5.9	0.03
Albumin (g/dL)		2.3 ± 0.7	2.4 ± 0.8	0.03
Charlson Score		2.4 ± 2.3	2.7 ± 2.6	0.04
Platelet Count (10 ³ /μL)		212.0 ± 115.7	58.5 ± 14.8	<0.001
Initial Modality	HD	193 (33%)	105 (19%)	<0.001
	CVV/DHF	345 (60%)	391 (72%)	
	SLED	26 (5%)	25 (5%)	
	Other	16 (2%)	23 (4%)	

Table 2.

Multivariate regression analysis for the primary outcome of 60-day mortality and secondary outcomes based on values of baseline platelets.

Outcome	Odds Ratio and 95% Confidence Interval
	Platelets < 100 x 10³/μL^a
60-day Mortality	1.60 (1.23 – 2.09)
28-day Mortality	1.55 (1.19 – 2.02)
1-year Mortality	1.46 (1.11 – 1.92)
Renal Recovery	0.56 (0.41- 0.75)
RRT Free Days	0.80 (0.68 – 0.95)
ICU Free Days	0.91 (0.81 – 1.02)
Hospital Free Days	0.94 (0.84 – 1.06)
Bleeding Event within 72 hours	1.10 (0.74 – 1.64)

OR = odds ratio

^aReference group was Platelets > 100 x 10³/μL

The adjusted model included age, gender, race, body mass index, albumin, modified SOFA score, and Charlson score

Table 3.

Multivariate regression analysis for primary outcome of 60-day mortality and secondary outcomes in those with a platelet decrease following RRT initiation.

Outcome	Odds Ratio with 95% Confidence Interval	
	Platelet Decrease ^a (Model 1 ^b)	Platelet Decrease ^a (Model 2 ^c)
60-day Mortality	1.51 (1.12 - 2.02)	1.48 (1.07 - 2.06)
28-day Mortality	1.30 (0.97 - 1.75)	1.26 (0.91 - 1.75)
1-Year Mortality	1.23 (0.92 - 1.63)	1.20 (0.88 - 1.63)
Renal Recovery	0.94 (0.68 - 1.29)	0.96 (0.70 - 1.32)
RRT Free Days	1.10 (0.92 - 1.31)	1.12 (0.95 - 1.32)
ICU Free Days	0.96 (0.89 - 1.03)	0.93 (0.88 - 1.00)
Hospital Free Days	0.88 (0.78 - 0.99)	0.89 (0.79 - 0.99)

OR = odds ratio

^aReference group was Platelet Increase by 0%.

^bModel 1: Age, Gender, Race, BMI, albumin, modified SOFA at admission, Charlson score, and baseline platelets

^cModel 2: Age, Gender, Race, BMI, albumin, modified SOFA at 72 hours, Charlson score, and baseline platelets

Table 4.

Multivariate regression analysis for 60-day mortality and secondary outcomes based on percent platelet decrease following RRT initiation in patients with a baseline platelet value $> 100 \times 10^3/\mu\text{L}$.

Outcome	Odds Ratio with 95% Confidence Interval	
	Platelet Decrease ^a (Model 1 ^b)	Platelet Decrease ^a (Model 2 ^c)
60-day Mortality	1.85 (1.21 - 2.83)	1.72 (1.08 - 2.73)
28-day Mortality	1.52 (0.98 - 2.34)	1.37 (0.85 - 2.22)
1-Year Mortality	1.26 (0.85 - 1.87)	1.13 (0.74 - 1.74)
Renal Recovery	0.67 (0.42 - 0.98)	0.67 (0.44 - 1.01)
RRT Free Days	1.10 (0.92 - 1.31)	1.12 (0.95 - 1.32)
ICU Free Days	0.93 (0.85 - 1.02)	0.91 (0.84 - 0.99)
Hospital Free Days	0.88 (0.75 - 1.02)	0.88 (0.76 - 1.03)

OR = odds ratio

^aReference group was Platelet Increase by 0%.

^bModel 1: Age, Gender, Race, BMI, albumin, modified SOFA at admission, Charlson score, and baseline platelets

^cModel 2: Age, Gender, Race, BMI, albumin, modified SOFA at 72 hours, Charlson score, and baseline platelets

Table 5.

Multivariate analysis to predict a decrease in platelets following RRT initiation

Variable	OR (95% CIs)	P value
Day 1 CRRT	1.49 (0.56 – 3.95)	0.4
Day 2 CRRT	1.08 (0.39 – 2.99)	0.9
AKI due to Liver Disease	1.63 (0.93 – 2.85)	0.09
Modified SOFA score	1.05 (0.995 – 1.11)	0.08
Baseline Platelets	1.004 (1.002 – 1.006)	< 0.001
Total Diafilters Lost	1.04 (0.91 – 1.18)	0.6

CRRT = continuous renal replacement therapy; OR = odds ratio

All covariates in the final model are reported below