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Therapeutic Plasma Exchange Is Associated With Improved Major Adverse Kidney Events in Children and Young Adults With Thrombocytopenia at the Time of Continuous Kidney Replacement Therapy Initiation

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OBJECTIVES: Therapeutic plasma exchange (TPE) has been shown to improve organ dysfunction and survival in patients with thrombotic microangiopathy and thrombocytopenia associated with multiple organ failure. There are no known therapies for the prevention of major adverse kidney events after continuous kidney replacement therapy (CKRT). The primary objective of this study was to evaluate the effect of TPE on the rate of adverse kidney events in children and young adults with thrombocytopenia at the time of CKRT initiation.

DESIGN: Retrospective cohort.

SETTING: Two large quaternary care pediatric hospitals.

PATIENTS: All patients less than or equal to 26 years old who received CKRT between 2014 and 2020.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We defined thrombocytopenia as a platelet count less than or equal to 100,000 (cell/mm^3) at the time of CKRT initiation. We ascertained major adverse kidney events at 90 days (MAKE90) after CKRT initiation as the composite of death, need for kidney replacement therapy, or a greater than or equal to 25% decline in estimated glomerular filtration rate from baseline. We performed multivariable logistic regression and propensity score weighting to analyze the relationship between the use of TPE and MAKE90. After excluding patients with a diagnosis of thrombotic thrombocytopenia purpura and atypical hemolytic uremic syndrome ($n = 6$) and with thrombocytopenia due to a chronic illness ($n = 2$), 284 of 413 total patients (68.8%) had thrombocytopenia at CKRT initiation (51% female). Of the patients with thrombocytopenia, the median (interquartile range) age was 69 months (13–128 mo). MAKE90 occurred in 69.0% and 41.5% received TPE. The use of TPE was independently associated with reduced MAKE90 by multivariable analysis (odds ratio [OR], 0.35; 95% CI, 0.20–0.60) and by propensity score weighting (adjusted OR, 0.31; 95% CI, 0.16–0.59).

CONCLUSIONS: Thrombocytopenia is common in children and young adults at CKRT initiation and is associated with increased MAKE90. In this subset of patients, our data show benefit of TPE in reducing the rate of MAKE90.

KEY WORDS: acute kidney injury; continuous kidney replacement therapy; thrombocytopenia; thrombocytopenia-associated multiple organ failure; thrombotic microangiopathy

Thrombocytopenia can be a clinical manifestation of microvascular thrombosis and has long been established as an independent risk factor for worsening organ function and mortality in critically ill patients

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KEY POINTS

Question: Does the rate of major adverse kidney events at 90 days (MAKE90) for children and young adults with thrombocytopenia at continuous kidney replacement therapy (CKRT) initiation who receive therapeutic plasma exchange (TPE) differ when compared with patients who do not receive TPE?

Findings: In this multicenter retrospective study of children and young adults with thrombocytopenia at the start of CKRT, the use of TPE concurrent with CKRT was associated with reduced MAKE90.

Meanings: Plasma exchange therapy may be a novel treatment option for avoiding long-term kidney morbidity in critically ill children and young adults with thrombocytopenia receiving CKRT.

(1, 2). Both mortality and acute kidney injury (AKI) rates are high in thrombocytopenic patients with multiple organ failure (3, 4). Studies from the Acute Renal Failure Trial Network show that thrombocytopenia prior to continuous kidney replacement therapy (CKRT) initiation is an independent risk factor for mortality and lack of renal recovery (5). Investigators have reported the benefit of therapeutic plasma exchange (TPE) in treating diseases characterized by thrombotic microangiopathy, such as thrombotic thrombocytopenia purpura (TTP) or atypical hemolytic uremic syndrome (aHUS) (6). Improvements in platelet count, severity of illness, and survival following TPE have been shown in patients with thrombocytopenia along with evidence of organ failure due to its ability to clear prothrombotic meditators and replace these with normal plasma (7).

The potential impact of TPE on mortality and kidney outcomes has not yet been explored, specifically in patients with thrombocytopenia and AKI, in the absence of a diagnosis of TTP and aHUS. Although investigators have reported declining platelet counts with CKRT (8), the frequency of thrombocytopenia before CKRT initiation is unknown. Therefore, using data from two large quaternary care pediatric centers, our primary study objective was to determine if there are differences in major adverse kidney events at 90 days (MAKE90) for patients with thrombocytopenia at CKRT initiation who receive TPE compared with those who do not receive TPE without a diagnosis of TTP or aHUS. We also sought to determine the frequency of thrombocytopenia at CKRT initiation. We tested the hypothesis that patients with thrombocytopenia at CKRT initiation will benefit from concomitant TPE therapy. Our primary outcome was MAKE90 and our secondary outcome was length of stay in CKRT patients with thrombocytopenia.

MATERIALS AND METHODS

Study Design

This is a retrospective cohort study of patients who received CKRT at two large quaternary care children's hospitals over a 6-year period. The study was approved by the Institutional Review Boards for Health Sciences Research at the two participating centers, Baylor College of Medicine ("Thrombocytopenia and Major Adverse Kidney Outcomes in Pediatric Patients who Underwent CRRT for Acute Renal Failure," protocol number H-47321, approval date April 9, 2020) and the University of Pittsburgh ("Thrombocytopenia and MAKE Outcomes in Patients who Received CRRT," protocol number 19070409, approval date October 15, 2019) in adherence to the Declaration of Helsinki. We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting study results (**Supplemental Fig. 1**, http://links.lww.com/CCX/B165). All patients who received CKRT in either the PICU or cardiac ICU at Texas Children's Hospital (TCH) or University of Pittsburgh Medical Center Children's Hospital of Pittsburgh (CHP) between 2014 and 2020 and were less than or equal to 26 years old at the time of ICU admission were included in the study. Patients with a diagnosis of TTP and aHUS were excluded as TPE is an already established therapy for these conditions (9). Patients with chronic thrombocytopenia were excluded as well. We determined the diagnosis of TTP, aHUS and chronic thrombocytopenia based on *International Classification of Diseases*, 9th Revision (ICD-9), *International Classification of Diseases*, 10th Revision (ICD-10) codes as well as manually screening all patient charts for physician documentation of the diagnoses. If a patient received more than one treatment course of CKRT during the hospital admission, only the first course was included in our analysis. Data

were extracted from the electronic health records at each center and managed using an online Research Electronic Data Capture database.

Variable Definitions

The variables that we included in the analyses have demonstrated previous prognostic performance for poor kidney and length of stay outcomes (10, 11). The primary indication for ICU admission was determined by individual patient chart review and placed into one of 10 categories (**Supplemental Table 1**, http://links.lww.com/CCX/B165). We defined baseline serum creatinine as the median of all creatinine values in the 6 months prior to hospital admission. If no serum creatinine was available prior to hospital admission, we imputed an estimated glomerular filtration rate (eGFR) of 100 mL/min per 1.73 m^2 and back calculated a reference serum creatinine based on the Schwartz equation as has been previously described (12, 13). We defined chronic kidney disease (CKD) by ICD-9 or ICD-10 coding. Thrombocytopenia was defined by a platelet count less than or equal to 100,000 (cell/mm^3) within 4 hours prior to CKRT initiation. Patients with thrombocytopenia developing after CKRT initiation were not included in the analysis of the effect of TPE on MAKE90. The validated Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score in the first 24 hours of admission and at the time of CKRT initiation were used to characterize the severity of illness (11). Given prior study results showing the association of methicillin-resistant *Staphylococcus aureus* (MRSA) infection with death in patients with thrombocytopenia along with evidence of organ failure (14), patients were deemed to be positive for MRSA if there was documented evidence of respiratory, blood, or urine infection at any point before or during their CKRT course. We did not have access to reliable data regarding participant race and ethnicity.

Methods Used for CKRT and TPE

At both centers, a dual-lumen hemodialysis catheter ranging in size from 7F to 15.5F depending on patient size was placed in all patients and CKRT was performed using the Prismaflex System (Baxter International, Deerfield, IL). At TCH, Prismasate or Prismasol solution (Baxter International) was used. Regional anticoagulation with anticoagulant citrate dextrose solution (Citra Labs, Braintree, MA) was titrated based on the TCH protocol for CKRT. At CHP, Phoxillum or Accusol solution (Baxter International) was used. Anticoagulation was achieved using citrate, heparin, or prostacyclin based on the CHP protocol for CKRT. At both centers, centrifugal TPE was performed using the Optima Spectra Apheresis System (Terumo, Lakewood, CO) via an independent catheter ranging from 7F to 15.5F depending on the patient's size or concurrent with CKRT therapy using fresh frozen plasma as replacement. Both centers similarly exchange 1.3–1.5 times the patient's calculated blood volume on day 1 of TPE, followed by a single volume exchange on subsequent days. Both centers have previously published their techniques for concurrent CKRT and TPE therapy (15, 16).

Study Outcomes

The primary outcome, MAKE90, is the composite outcome of death, dialysis, or incomplete kidney recovery 90 days after the initiation of CKRT (17). Given that death is a competing endpoint, MAKE as a composite endpoint has previously been recommended (18). We defined incomplete kidney recovery as a greater than or equal to 25% decline in eGFR from baseline at 90 days of CKRT initiation, determined from the last known serum creatinine within 90 days of CKRT initiation as compared with the patient's baseline or reference value. If a patient died, the death endpoint was met, but not incomplete kidney recovery or dialysis dependency. Additionally, if a patient met the dialysis endpoint, they were also considered to have incomplete kidney recovery. The dialysis endpoint included CKRT, intermittent hemodialysis, or peritoneal dialysis. We chose to ascertain MAKE at 90 days given that this is the time when CKD is diagnosed after AKI (19).

Statistical Analyses

Continuous variables are presented as medians (interquartile range [IQR]) and categorical variables are presented as numbers (percentages). Mann-Whitney rank-sum and chi-square tests were used to compare continuous and categorical variables, respectively. Variables identified by univariable regression with a p value of less than 0.2 were included in a multivariable logistic regression model to determine factors independently associated with MAKE90 with a corresponding

odds ratio (OR) and 95% CI. In the patients with thrombocytopenia, in order to account for those variables that predict a higher likelihood of receiving TPE, a propensity score-weighted analysis was performed. Patients were stratified by the receipt of TPE using 1:1 matching using the R package MatchIT, Vienna, Austria (20). The independent covariates for the propensity model included: PELOD-2 at ICU admission, PELOD-2 at CKRT start, need for extracorporeal membrane oxygenation therapy, body surface area, MRSA, age, sex, CKD, and baseline serum creatinine. We allowed a tolerance by setting a caliper of 0.3, thereby matching between patients based on the receipt of TPE exclusively if they were within 0.3 SDs of a propensity score away from each other. Additionally, we conducted subgroup analyses whereby we evaluated the association of TPE and MAKE90 individually among patients with thrombocytopenia admitted with one of the five most common primary indications for admission.

Negative binomial regression was used to determine differences in ICU length of stay for patients with thrombocytopenia who received TPE when compared with those that did not. A corresponding rate ratio was reported. For each final model, p values of less than or equal to 0.05 were considered statistically significant. All statistical analyses were performed using STATA 16.1 (Stata Corp, College Station, TX), Python Version 3.7.3 (Python Software Foundation, Beaverton, OR), and R software Version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The entire cohort included 421 individual patients who received CKRT at TCH and CHP. Six patients were excluded due to a diagnosis of TTP or aHUS. Two patients were excluded due to known thrombocytopenia due to a chronic underlying illness (**Fig. 1**). A total of 284 of 413 patients (68.8%) met criteria for thrombocytopenia at CKRT initiation. **Supplemental Table 1** (http://links.lww.com/CCX/B165) shows the primary reasons for ICU admission with shock as the most frequent principal indication for admission. Baseline demographics and clinical characteristics for the 284 patients that met criteria for thrombocytopenia at CKRT initiation are summarized in **Table 1**. Patients were a median age of almost 6 years with an equal distribution of male and female. One or more prior creatinine values were available in the 6 months prior to hospital admission in 184 patients (64.8%) with thrombocytopenia. For 100 patients, no creatinine values were available prior to admission and, therefore, an estimate of baseline creatinine was calculated as was previously described (12, 13). There was a small proportion of patients with CKD (7.8%). The median (IQR) PELOD-2 score at admission was 6 (4–9) and at CKRT initiation was 10 (7–12). Whereas PELOD-2 scores at the time of ICU admission were similar when comparing patients based on receiving TPE, PELOD-2 scores at the time of CKRT initiation were greater in those that received TPE. **Supplemental Table 2** (http://links.lww.com/CCX/B165) shows the baseline demographics for the entire patient cohort.

CKRT and TPE Treatments

The majority of patients received CKRT with the primary indications of fluid overload and/or AKI (**Supplemental Table 3**, http://links.lww.com/CCX/B165). The most prescribed treatment mode was continuous venovenous hemodiafiltration using a HF1000 hemofilter set (**Supplemental Table 4**, http://links.lww.com/CCX/B165). In patients with thrombocytopenia, the median prescribed CKRT doses ranged from 1,200 to 6,000 mL/hr/1.73 m^2 with a median dose of 2,000 mL/hr/1.73 m^2. The median (IQR) duration of CKRT was 9 days (3–21 d). No patients received TPE prior to the initiation of CKRT. The median time from ICU admission to the start of CKRT at TCH did not differ as compared with CHP ($p = 0.16$) with a combined center median (IQR) time to initiation of CKRT of 3 days (1–10 d). The median time from CKRT initiation to the start of TPE was similar between centers ($p = 0.71$) with a combined center median (IQR) time to initiation of TPE of 2 days (0–6 d). The number of patients that received TPE with CKRT was similar during the years 2014 through 2020 (**Supplemental Fig. 2**, http://links.lww.com/CCX/B165). The combined median (IQR) duration of TPE therapy was 5 days (2–8 d).

The Association Between MAKE90 and TPE in Patients With Thrombocytopenia

Overall, MAKE90 occurred in 69.0% of patients with thrombocytopenia and 56.6% of patients without thrombocytopenia ($p = 0.01$). When compared with

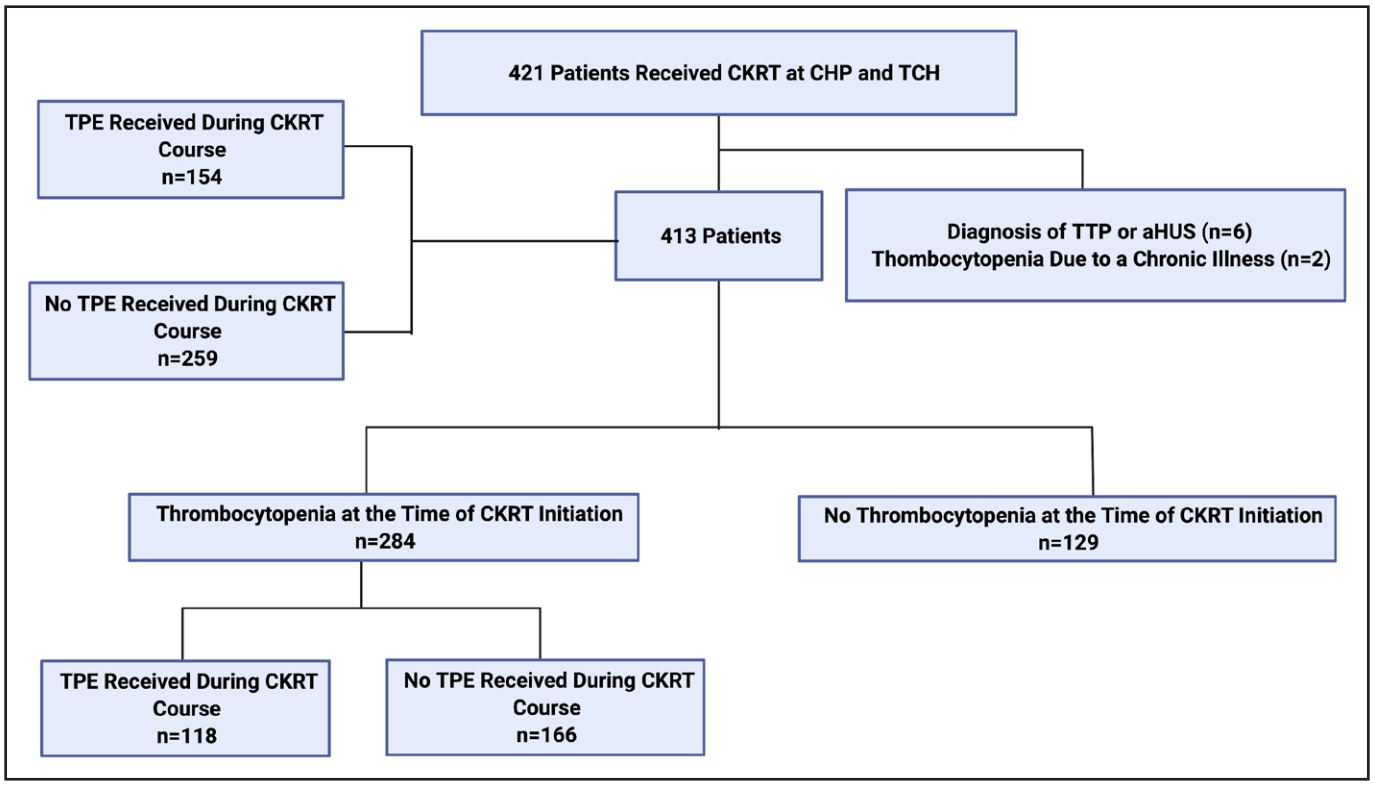

Figure 1. A flow diagram of patients included in the study. aHUS = atypical hemolytic uremic syndrome, CHP = Children's Hospital of Pittsburgh, CKRT = continuous kidney replacement therapy, TCH = Texas Children's Hospital, TPE = therapeutic plasma exchange, TTP = thrombotic thrombocytopenia purpura.

thrombocytopenic patients who did not receive TPE, patients with thrombocytopenia receiving TPE had a lower rate of MAKE90 (55.9% vs 78.3%; $p < 0.001$) (**Table 2**). The univariable analysis for MAKE90 identified baseline serum creatinine, CKD, PELOD-2 score at CKRT initiation, TPE, and MRSA infection (**Supplemental Table 5**, http://links.lww.com/CCX/B165) for inclusion in the multivariable regression. TPE was independently associated with lower odds of MAKE90 (OR, 0.35; 95% CI, 0.20–0.60; $p < 0.001$) (**Table 3**). Additionally, propensity score weighting analysis was used to estimate MAKE90 accounting for variables that predicted a higher likelihood of receiving TPE (**Supplemental Figs. 3** and **4**, http://links.lww.com/CCX/B165). **Table 4** shows differences in covariates based on the receipt of TPE before and after propensity score matching. After propensity score matching, all covariates showed no difference between treatment groups, thus median propensity scores became comparable. A total of 210 patients were included in the propensity-adjusted multivariable logistic regression. The adjusted OR for MAKE90 in the propensity analysis was 0.31 (95% CI, 0.16–0.59; $p < 0.001$).

In order to determine if the primary study outcome differed based on the primary reason for admission, we examined the association of TPE with MAKE90 in patients with thrombocytopenia separately by the five most frequent primary indications for admission: shock, cardiac, hematology/oncology, respiratory, and liver failure (Supplemental Table 1, http://links.lww.com/CCX/B165). In patients with shock, liver failure, or cardiac disease, TPE was associated with a lower odds of MAKE90 (**Supplemental Tables 6–8**, http://links.lww.com/CCX/B165; **Fig. 2**). However, TPE was not significantly associated with MAKE90 in those patients admitted with a primary oncologic, hematologic, or respiratory diagnosis (**Supplemental Tables 9** and **10**, http://links.lww.com/CCX/B165; Fig. 2).

We questioned if prior patient characteristics such as a preexisting diagnosis of CKD or a lack of new onset thrombocytopenia might influence our study results. Therefore, we conducted two sensitivity analyses. In the first, we excluded patients with a prior diagnosis of CKD ($n = 22$) to determine the association of TPE with MAKE90 in patients with

TABLE 1.
Baseline Characteristics of Patients With Thrombocytopenia at the Time of Continuous Kidney Replacement Therapy Initiation

Characteristics[a]	(*n* = 284)	TPE (*n* = 118)	No TPE (*n* = 166)	*p*
Age at ICU admission (mo)	69 (13–168)	81 (16–187)	57 (9–158)	0.05
Sex (female)	145 (51.1)	63 (53.4)	82 (49.4)	0.51
Body surface area (m^2)	0.78 (0.47–1.41)	0.81 (0.50–1.66)	0.74 (0.37–1.33)	0.03
Baseline serum creatinine (mg/dL)	0.30 (0.13–0.60)	0.30 (0.15–0.60)	0.25 (0.08–0.50)	0.05
Chronic kidney disease	22 (7.8)	4 (3.4)	18 (10.8)	0.02
PELOD-2 score at ICU admission	6 (4–9)	6 (3–10)	6 (4–9)	0.83
PELOD-2 score at CKRT initiation	10 (7–12)	10 (8–12)	9 (7–11)	< 0.001
Platelet count at CKRT initiation ($cell/mm^3$)	64 (46–85)	51 (33–72)	48 (33–67)	0.40
Extracorporeal membrane oxygenation during ICU admission	53 (18.7)	27 (16.3)	26 (22.0)	0.22
Methicillin-resistant *Staphylococcus aureus* during ICU admission	32 (11.3)	8 (6.8)	24 (14.5)	0.04

CKRT = continuous kidney replacement therapy, PELOD-2 = Pediatric Logistic Organ Dysfunction-2, TPE = therapeutic plasma exchange.

[a]Data are expressed as median (interquartile range) or *n* (%).

TABLE 2.
Incidence of Major Adverse Kidney Events at 90 Days in Patients With Thrombocytopenia

Outcome	All Patients With Thrombocytopenia (*n* = 284), *n* (%)	TPE (*n* = 118), *n* (%)	No TPE (*n* = 166), *n* (%)	*p*
Major adverse kidney events at 90 d	196 (69.0)	66 (55.9)	130 (78.3)	< 0.001
Death at 90 d	132 (46.5)	47 (39.8)	85 (51.2)	0.05
Dialysis at 90 d	33 (11.6)	10 (8.5)	23 (13.9)	0.16
Estimated glomerular filtration rate at 90 d	64 (22.5)	19 (16.1)	45 (27.1)	0.02

TPE = therapeutic plasma exchange.

thrombocytopenia without a diagnosis of CKD preceding CKRT initiation. The results were similar to when we included patients with CKD whereby TPE was independently associated with reduced MAKE90 (OR, 0.33; 95% CI, 0.19–0.58; $p < 0.001$) as shown in **Supplemental Tables 11** and **12** (http://links.lww.com/CCX/B165). We also repeated the unadjusted and adjusted regression analyses including patients that did not meet the predefined threshold for thrombocytopenia (n = 129). In contrast to patients with thrombocytopenia, TPE was not significantly associated with MAKE90 in patients without thrombocytopenia at the time of CKRT initiation (**Supplemental Tables 13** and **14**, http://links.lww.com/CCX/B165).

Given that TP is thought to be efficacious in thrombotic microangiopathy to due replenishing ADAMTS-13 (a Distntegrin and Metalloproteinase with a Thrombospondin Type 1 motif, member 13), we questioned if prescribers were using ADAMTS-13 levels to determine the need for TPE (21). A level was obtained in 63 patients (22.2%) with thrombocytopenia with a median value of 49%. Of those patients where an ADAMTS-13 level was obtained, 49 (77.8%) received TPE and 14 (22.2%) did not. There was no difference in ADAMTS-13 levels when comparing

TABLE 3.
Multivariable Regression Analysis for Major Adverse Kidney Events at 90 Days in Patients With Thrombocytopenia

Characteristic ($n = 284$)	OR (95% CI); p
Baseline serum creatinine	1.30 (0.79–2.13); 0.31
Chronic kidney disease	7.51 (0.94–59.73); 0.06
Pediatric Logistic Organ Dysfunction-2 score at CKRT initiation	1.10 (1.02–1.19); 0.02
Therapeutic plasma exchange during CKRT course	0.35 (0.20–0.60); < 0.001
Methicillin-resistant *Staphylococcus aureus* during ICU admission	1.87 (0.71–4.91); 0.21

CKRT = continuous kidney replacement therapy, OR = odds ratio.

patients based on the receipt of TPE (p = 0.82). In those patients who received TPE and an ADAMTS-13 value was reported, all activity levels were obtained before TPE initiation.

The Association Between TPE and ICU Length of Stay in Patients With Thrombocytopenia

In order to account for the potential bias of early mortality, only those individuals who left the ICU alive (n = 166) were included in a negative binomial regression analysis assessing factors independently associated with ICU length of stay. Baseline serum creatinine and MRSA were significantly associated with a longer ICU length of stay in a univariable analysis and, therefore, included in the regression analysis. Since TPE was not significant, it was forced into the model (**Supplemental Table 15**, http://links.lww.com/CCX/B165). For patients with thrombocytopenia, the median length of stay for patients that received TPE (20 d) did not differ when compared with those that did not (17 d) (p = 0.78).

DISCUSSION

In this first study to date exploring MAKE outcomes in children and young adults after CKRT, the use of TPE in patients with thrombocytopenia at CKRT start was associated with a significant decrease in MAKE90. The identification of therapies for AKI in both adults and children is a major research priority. For patients receiving CKRT, there has been an increased attention to the association of fluid balance and outcomes including kidney disease progression, dialysis dependence, and mortality (22). However, there are no available direct therapeutic options to modify the risk of adverse kidney outcomes or death once patients begin CKRT. Plasma exchange therapy may be a novel treatment option for avoiding long-term kidney morbidity in a subset of critically ill patients with thrombocytopenia receiving CKRT. Additionally, in this patient cohort, although those prescribed TPE had a greater severity of illness score at the time of CKRT initiation when compared with those not prescribed TPE (p < 0.001), there was no difference in ICU length of stay when comparing patients based on the receipt of TPE.

For critically ill patients with TTP or aHUS, the use of TPE has become a standard therapy (23, 24). There is emerging evidence of the efficacy of TPE for children and adults with thrombocytopenia with evidence of organ failure (4, 14, 21, 25, 26). An analysis of data from a large registry of children with thrombocytopenia and organ failure reveals that 47.6% of patients meeting these criteria have AKI requiring kidney replacement therapy (4). At our centers, we consider the use of TPE for patients with evidence of organ failure in at least two organ systems and thrombocytopenia. We do not have a defined ADAMTS-13 level for which we start TPE, as evidenced by the lack of difference in ADAMTS-13 levels when comparing patients based on the receipt of TPE found in this study.

Thrombocytopenia was common prior to CKRT in our study population. The mechanism of benefit provided by TPE shown in our study results requires further investigation. It is known that microvascular thrombosis clinically manifests as thrombocytopenia. The injurious cycle of microvascular thrombosis can be exacerbated by the presence of ultra-large von Willebrand factor (ULVWF) clusters which promote clotting and consumption (24, 27). TPE is standard therapy for patients with TTP and aHUS as it replaces ADAMTS-13, a metalloproteinase that cleaves ULVWF into less thrombogenic forms and removes ULVWF clusters (9). The known pathologic effects of the release of cell-free plasma hemoglobin with extracorporeal therapies may offer another potential beneficial mechanism of TPE seen in our study results (28–32), given reports of the utility of TPE in the removal of cell-free plasma hemoglobin (33–35). However, additional

TABLE 4.

Characteristics of Patients With Thrombocytopenia Before and After Propensity Score Matching

Characteristic	Before Propensity Score Matching			1:1 Matched		
	No TPE	TPE	Unadjusted *p*	No TPE	TPE	Matched *p*
Number of patients	166	118		105	105	
Age, mo, median (IQR)	57 (9–158)	81 (16–187)	0.05	75 (22–158)	72 (15–175)	0.54
Body surface area, m^2, median (IQR)	0.74 (0.37–1.33)	0.81 (0.50–1.66)	0.03	0.81 (0.51–1.34)	0.78 (0.49–1.46)	0.67
Sex (% female)	82 (49.4)	63 (53.4)	0.51	52 (49.5)	49 (46.7)	0.78
Methicillin-resistant *Staphylococcus aureus* (%)	24 (14.5)	8 (6.8)	0.04	7 (6.7)	8 (7.6)	1
Extracorporeal membrane oxygenation (%)	27 (16.3)	26 (22.0)	0.22	20 (19.0)	23 (21.9)	0.73
Baseline serum creatinine, mg/dL, median (IQR)	0.25 (0.08–0.50)	0.30 (0.15–0.60)	0.05	0.25 (1.12–0.50)	0.30 (0.15–0.60)	0.22
Chronic kidney disease (%)	18 (10.8)	4 (3.4)	0.02	3 (2.9)	4 (3.8)	0.28
PELOD-2 score at ICU admission, median (IQR)	6 (4–9)	6 (3–10)	0.83	7 (4–10)	6 (3–10)	0.28
PELOD-2 score at continuous kidney replacement therapy initiation, median (IQR)	9 (7–11)	10 (8–12)	< 0.001	10 (7–12)	10 (8–12)	0.81

IQR = interquartile range, PELOD-2 = Pediatric Logistic Organ Dysfunction-2, TPE = therapeutic plasma exchange.

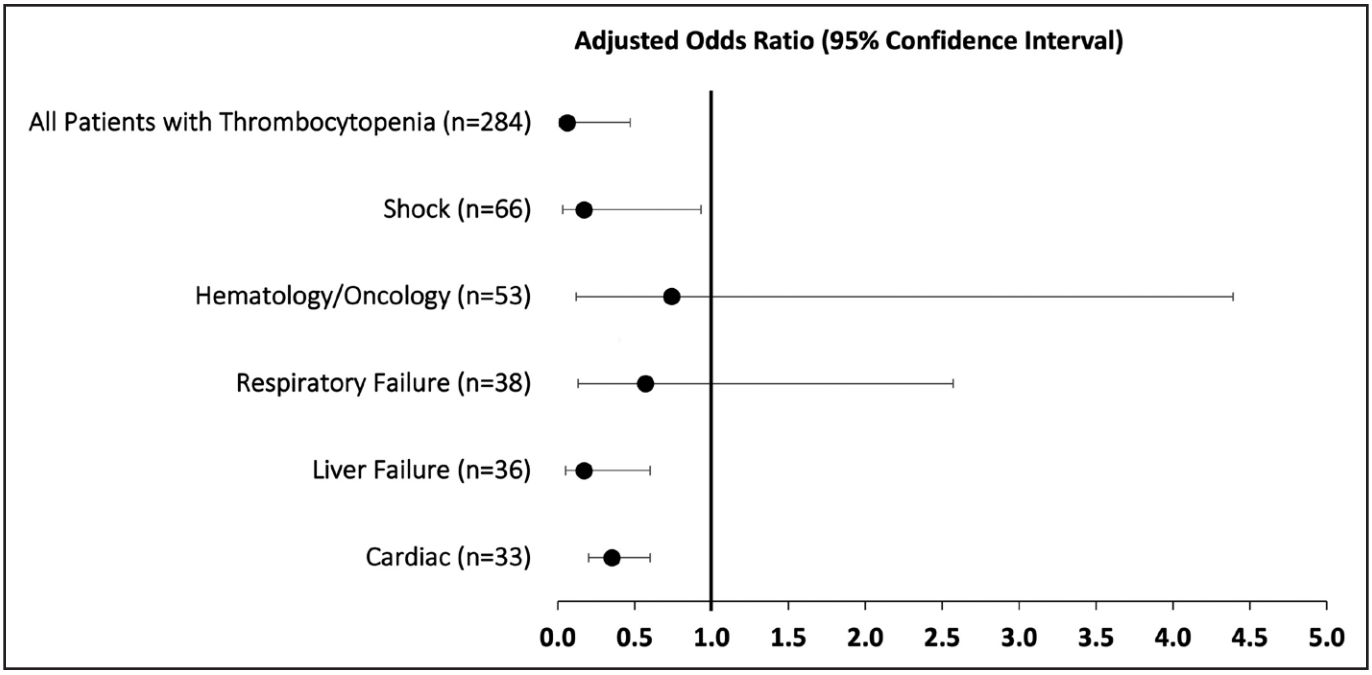

Figure 2. A *forest plot* showing the adjusted odds ratio (OR) (95% CI) for major adverse kidney events at 90 d (MAKE90) for all patients with thrombocytopenia and patients with thrombocytopenia separated by the five most common primary indications for admission. Therapeutic plasma exchange (TPE) was associated with a lower odds of MAKE90 in patients with shock (OR, 0.17; 95% CI, 0.05–0.60; $p = 0.006$), liver failure (OR, 0.17; 95% CI, 0.03–0.93; $p = 0.04$), or cardiac disease (OR, 0.06; 95% CI, 0.01–0.47; $p = 0.008$). However, TPE was not associated with MAKE90 in those patients admitted with a primary respiratory (OR, 0.74 [0.12–4.39]; 0.74) or oncologic/hematologic (OR, 0.58 [0.13–2.57]; 0.47) diagnosis.

work is needed to determine any potential role of TPE on levels of cell-free plasma hemoglobin as a contributor to improved kidney outcomes in dialysis patients with thrombocytopenia.

When separated by primary reason for ICU admission, the association of TPE with MAKE90 differed based on diagnosis. In patients admitted for shock, liver failure, or cardiac disease, TPE was associated with a lower odds of MAKE90, whereas there was no significant association of TPE with MAKE90 in patients admitted with other diagnoses. Of the 36 patients admitted with liver failure, two patients received a liver transplant prior to the initiation of CKRT. It is possible that we may not have seen the same benefit of TPE in liver failure patients if the majority of our cohort had received CRRT after liver transplantation. Liver transplant itself can result in transient thrombocytopenia due to reasons such as infection, sequestration, or medications (36). The effect of TPE on MAKE90 based on the primary indication for ICU admission requires exploration in future studies.

Our study has limitations. Given the retrospective nature of our study, it is possible that improvements in MAKE90 outcomes were due to unaccounted confounders unrelated or related to TPE. Both centers have extensive experience with CKRT and TPE, making our results potentially not generalizable to other centers that use these therapies less commonly. We did not control for factors in our study such as the timing of TPE initiation, duration of therapy, monitoring during treatment, or the use of TPE in tandem with CKRT which may all impact the beneficial effect of TPE in our study cohort. In addition, the relatively smaller incidence of TPE in the cohorts of patients showing no significant association of therapy with MAKE90 may have impacted the results related to power considerations. Importantly, we did not monitor trends in markers of microvascular thrombosis or hemolysis. Future investigations should quantify changes in laboratory values such as ADAMTS-13, von Willebrand factor, and cell-free plasma hemoglobin in patients with thrombocytopenia receiving CKRT with and without TPE. We did not have access to changes in platelet count values during CKRT or TPE to determine a potential association of changes in platelet count with MAKE90.

Despite these limitations, we have shown, using multivariable regression and propensity score weighting in a relatively large pediatric CKRT dataset, the

potential benefits of TPE for preventing MAKE outcomes at 90 days. There is a need for prospective data collection exploring potential mechanisms of benefit for TPE in this patient population. Future investigations should examine the impact of TPE on patients that develop thrombocytopenia after CKRT initiation. Furthermore, future studies exploring the questions we proposed in our study should be considered at centers that do not readily use TPE, whereby TPE initiation resources with a clearly defined protocol for implementation are provided. Given the increasing ease and published safety of providing TPE in tandem with CKRT (15, 16), our findings further support the need to explore the use of TPE in patients with thrombocytopenia receiving CKRT in a larger prospective randomized multicenter study.

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