# Limited Role of Plasma Exchange in Multiple Myeloma-Associated Acute Kidney Injury: Chemotherapy as the Cornerstone of Renal Recovery

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**ABSTRACT**

Acute kidney injury (AKI) is a common and serious complication in newly diagnosed multiple myeloma (MM), often causing dialysis and impairing treatment. Although modern chemotherapy improves renal function and survival, the benefit of adding prophylactic plasma exchange (PE) remains uncertain. This study investigates its effect on renal recovery and treatment response. A total of 47 MM patients with AKI were retrospectively analyzed. Seventeen patients received prophylactic PE alongside chemotherapy, while thirty received chemotherapy alone. Renal function, dialysis status, and treatment response were assessed over two chemotherapy cycles.In the PE group, median serum creatinine decreased significantly from 3.1 to 1.7 mg/dL (p= 0.002). Median reductions were also observed in free light chain (–202 mg/dL, p= 0.009) and heavy chain levels (–2959 mg/dL, p= 0.013). Dialysis independence was achieved in 50% of PE-treated patients compared to 16.7% in the non-PE group (p= 0.545). A strong positive correlation was identified between the number of PE sessions and creatinine improvement (r = 0.795, p= 0.006). Although bortezomib-based regimens yielded greater early reductions in creatinine (p= 0.021), this difference was no longer significant after the second cycle. Prophylactic PE was associated with rapid biochemical improvement and higher dialysis independence rates, particularly in patients with a high circulating light chain burden. However, its long-term benefit appears limited. Chemotherapy – particularly proteasome inhibitors and anti-CD38 monoclonal antibodies – remains the primary driver of renal recovery in MM-associated AKI, supporting a selective rather than routine use of PE.

**Keywords:** Multiple myeloma, Acute kidney injury, Plasma exchange, Bortezomib-based therapy; Dialysis dependency

## INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells, often leading to organ damage, particularly acute kidney injury (AKI). Renal impairment is a well-established myeloma-defining event, with light chain cast nephropathy being the predominant cause.[1] Approximately 50% of newly diagnosed MM patients develop AKI, and 10–15% require dialysis[2-4], significantly affecting overall survival (OS) and treatment feasibility. The mechanisms underlying MM-related AKI are multifactorial, involving free light chain (FLC) deposition, hypercalcemia, dehydration, and nephrotoxic agents.[2,3,5] Given its substantial impact on prognosis, optimizing renal recovery remains a critical aspect of MM management.[6,7]

Therapeutic plasma exchange (TPE) has been investigated as a potential adjunctive therapy for MM-associated AKI due to its ability to rapidly reduce circulating FLC levels and alleviate nephrotoxicity.[8] Although early studies suggested that TPE might facilitate renal recovery, randomized controlled trials have reported conflicting results, with some demonstrating improved renal outcomes[9], while others, such as the largest randomized

controlled trial by Clark et al., found no significant improvement in OS or long-term dialysis independence compared to standard therapy.[10] Consequently, the routine use of TPE remains controversial, and its role in MM-associated AKI is not firmly established in current guidelines.

Modern myeloma therapies, particularly proteasome inhibitors and anti-CD38 monoclonal antibodies, have significantly improved renal outcomes in MM patients, raising further questions about the necessity of TPE. Bachmann, et al. demonstrated that all tested regimens improved renal function, yet lenalidomide-based regimens carried a higher risk of renal deterioration.[11] These findings underscore the need for renal-friendly treatment strategies, while also raising questions about whether TPE retains any clinical utility in the era of modern MM therapies. Given these advancements, the role of TPE in MM-associated AKI remains uncertain. A critical question is whether a subset of patients—particularly those with severe FLC-driven nephropathy—might still derive benefit from TPE, despite the efficacy of targeted therapies.

Recent advancements have introduced plasma-free plasmapheresis techniques as an alternative to traditional TPE, utilizing albumin-based replacement solutions instead of fresh frozen plasma to minimize transfusion-related complications[12], with Vural, et al. demonstrating that the use of only fresh frozen plasma is associated with a significantly higher complication rate compared to albumin-based solutions.[13] Emerging evidence suggests that this approach not only reduces FLC burden but also attenuates key inflammatory mediators, such as vascular endothelial growth factor and interleukin-6, which are implicated in MM progression and renal injury.[12] Additionally, sequential chemotherapy combined with plasma-free plasmapheresis has demonstrated efficacy in lowering β2-microglobulin levels and improving renal function, potentially reducing dialysis dependency and enhancing treatment outcomes.[12]

This study aims to evaluate the real-world impact of early TPE on renal function and dialysis dependency in newly diagnosed MM patients with AKI. Specifically, we compare renal recovery dynamics between patients who received early TPE and those managed with standard chemotherapy alone. By incorporating plasma-free plasmapheresis into the analysis, we also explore the feasibility of alternative extracorporeal approaches. Our findings may provide insight into whether TPE has a meaningful role in the current treatment landscape or if it should be reconsidered in favor of more effective renal recovery strategies.

## PATIENTS AND METHODS

### *Study Design*

This retrospective study investigated the impact of TPE on renal outcomes and treatment responses in newly diagnosed patients with MM and AKI. The intervention was implemented as a supportive or early approach to mitigate further renal deterioration in the absence of hyperviscosity syndrome. Ethical approval was granted by the institutional review board, and all procedures complied with the principles outlined in the Declaration of Helsinki. Informed consent was obtained from all participants. Although non-randomized, this study offers valuable real-world insights into clinical practice, providing a pragmatic perspective on the potential role of TPE in the management of AKI in MM patients.

### *Patient Selection*

Eligible patients were identified from institutional medical records. Inclusion criteria included a diagnosis of MM according to the International Myeloma Working Group criteria[14], AKI defined in accordance with Kidney Disease Improving Global Outcomes (KDIGO) standards.[15] Exclusion criteria encompassed the presence of hyperviscosity syndrome, comorbidities significantly impacting survival (e.g., advanced cardiac or hepatic insufficiency), or concurrent enrollment in other interventional trials.

Patients with severe comorbidities (e.g., advanced cardiac or hepatic insufficiency) were excluded to minimize the risk of TPE-related complications such as hemodynamic instability, bleeding, or electrolyte imbalance and to ensure that renal outcomes reflected treatment effects rather than comorbidity-associated confounders.

Early TPE was initiated in patients with newly diagnosed MM who presented with severe AKI (KDIGO Stage 2-3), markedly elevated serum FLC levels, or strong clinical suspicion of cast nephropathy, as assessed by the treating hematology team.

### *Plasma Exchange Procedure*

TPE was integrated into the treatment protocol using the Spectra Optia and Haemonetics MCS+ Apheresis Systems. Replacement fluids consisted of 4% human albumin, and saline. Total blood volume was estimated using Gilcher's Rule of 5, incorporating sex and body composition to account for differences in vascularization, while plasma volume was calculated based on total blood volume and hematocrit to ensure precise TPE prescriptions.[16,17] The exchange volume is typically set at 1 to 1.5 times the estimated plasma volume.

The frequency and total number of TPE sessions were individualized according to renal and biochemical response patterns. Decisions were guided by daily serum creatinine trends, serial measurements of the involved FLC when available, and the patient's overall clinical condition. Sessions were adjusted based on response, and treatment was generally discontinued once a clear improvement in renal or biochemical parameters was observed, or when no further benefit was evident.

Sessions were conducted daily or every other day, with the goal of achieving a > 50% reduction in serum FLC levels or significant improvements in renal function, such as decreases in serum creatinine. Chemotherapy was initiated shortly after the initial TPE sessions once clinical stability and adequate venous access were achieved, with timing individualized to minimize potential drug clearance during early exchanges. Importantly, this approach did not result in any treatment delay. For monoclonal antibody–based regimens (e.g., daratumumab), infusion timing was arranged after completion of TPE sessions to avoid potential drug removal during the procedure. TPE was typically completed within 7 days and was administered alongside bortezomib-based, lenalidomide-based, or daratumumab-based chemotherapy, with dose adjustments tailored to renal function. TPE discontinuation decisions were guided by clinical and laboratory improvements, as determined by the treating physician.

### *Data Collection*

Data were collected retrospectively from medical records, including demographic details, baseline renal function [serum creatinine and glomerular filtration rate (GFR)], and hematologic response rates.

GFR was estimated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[18] Baseline creatinine was defined as the lowest documented serum creatinine value within the three months preceding MM diagnosis, when available, or otherwise as the most recent stable measurement prior to presentation. Chronic kidney disease unrelated to MM (such as diabetic nephropathy, hypertensive nephropathy, or other chronic glomerulopathies) was excluded based on clinical history, laboratory parameters, imaging findings, and renal biopsy results when available.

Clinical parameters such as albuminuria, proteinuria, oliguria, dialysis dependency, and AKI severity (Stage 1-3) were recorded at baseline. Creatinine dynamics and treatment responses were assessed post-treatment to evaluate changes relative to baseline values.

### *Study Endpoints*

The primary focus of the study was to evaluate the impact of TPE on renal function, specifically changes in serum creatinine levels. Additionally, the study aimed to assess the effect of TPE on dialysis dependency rates, providing critical insights into its potential role in improving renal outcomes. Secondary endpoints included hematologic response rates (≥partial response [PR] or <PR) and the occurrence of adverse events associated with TPE.

## Statistical Analyses

All statistical analyses were conducted using SPSS Statistics for macOS, Version 27.0 (IBM Corp., Armonk, NY, USA), with complementary analyses performed in Python 3.9.6. The Kolmogorov-Smirnov test was used to assess the normality of

continuous variables. Group comparisons for normally distributed variables were performed using the Independent Samples t-test, while the Mann-Whitney U Test was applied for non-normally distributed data.

Categorical variables were analyzed using Fisher's Exact Test or Pearson's Chi-Square Test, depending on the expected cell counts. Changes in renal function and immunoglobulin levels before and after treatment were evaluated using the Wilcoxon Signed-Rank Test, and the Related-Samples McNemar Change Test was employed for paired categorical comparisons, such as treatment response dynamics.

To compare creatinine dynamics across clinical parameters, including albuminuria, proteinuria, oliguria, dialysis status, and AKI severity, non-parametric tests were used: the Mann-Whitney U Test for two-group comparisons and the Kruskal-Wallis Test for multi-group comparisons. Statistical significance was defined as a two-sided p-value of $< 0.05$.

***Ethical approval:*** Ethics committee approval was obtained for the conduct of the study (University of Health Sciences, Antalya Training and Research Hospital, date, 25 August 2022; No: 16/5). The study was conducted by the 1964 Declaration of Helsinki and subsequent revisions.

## RESULTS

A total of 47 patients with newly diagnosed MM and AKI were included in the study, with 17 undergoing TPE and 30 not receiving the intervention. Patients in the plasma exchange (PE) group were significantly younger than those in the non-PE group (median age: 62 vs. 70 years; p= 0.037). No significant differences were observed between the groups in terms of gender distribution, comorbidities (diabetes mellitus, hypertension, coronary artery disease), or baseline renal function markers, including serum creatinine (p= 0.406), urea (p= 0.203), and GFR (p= 0.308). Although advanced AKI (Stage 3) was more frequent in the PE group (64.7% vs. 43.3%), this difference was not statistically significant (p= 0.168). Renal biopsy was performed in 7 patients, while rectal biopsy was performed in 4 patients to further investigate the underlying pathology. A comprehensive summary of baseline characteristics is provided in Table 1.

### *Impact of Plasma Exchange on Renal and Immunoglobulin Parameters*

PE led to significant reductions in renal and immunoglobulin parameters. Median serum creatinine levels decreased by 0.5 mg/dL (p= 0.002), heavy chain levels by 2959 mg/dL (p= 0.013), and FLC levels by 202 mg/dL (p= 0.009) (Table 2). Additionally, dialysis independence was achieved in 50% of patients in the PE group compared to 16.7% in the non-PE group, although this difference did not reach statistical significance (p= 0.545), potentially due to the limited sample size. Importantly, TPE was well tolerated, with no serious or life-threatening complications observed in our cohort.

Patients in the PE group achieved their best treatment response slightly earlier (median: 2 months; range: 1-6 months) compared to the non-PE group (median: 3 months; range: 1-13 months). In contrast, the best serum creatinine response occurred slightly later in the PE group (median: 3 months; range: 1-12 months) than in the non-PE group (median: 2 months; range: 1-10 months). These differences in response times between the groups were not statistically significant.

A strong positive correlation was identified between the number of TPE sessions and the improvement in serum creatinine levels (r= 0.795, p = 0.006). However, no significant correlations were observed between the number of TPE sessions and changes in FLC or heavy chain levels (Table 3).

### *Treatment Response Dynamics*

In the PE Group (n= 17), a comparison of treatment responses between the first and second chemotherapy cycles (≥PR and <PR) showed no statistically significant differences in response distributions. The Related-Samples McNemar Change Test supported the null hypothesis, indicating an equal likelihood of response distributions across chemotherapy cycles (p= 1.000) (Figure 1A). These findings suggest that TPE did not significantly influence treatment response dynamics during the initial phases of therapy in this cohort.

**Table 1.** Baseline demographics and clinical characteristics stratified by plasma exchange status

| Variables | | Plasma Exchange Performed n (%) or Median (min-max) | Plasma Exchange Not Performed n (%) or Median (min-max) | Total n (%) or Median (min-max) | p-value |
|---|---|---|---|---|---|
| Age (year) | | 62 (32-91) | 70 (43-86) | 67 (32-91) | 0.037[a] |
| Gender | Female | 5 (29.4) | 8 (26.7) | 13 (27.7) | 1.000[b] |
| | Male | 12 (70.6) | 22 (73.3) | 34 (72.3) | |
| Diabetes mellitus | No | 16 (94.1) | 24 (80.0) | 39 (84.8) | 0.396[b] |
| | Yes | 1 (5.9) | 6 (20.0) | 7 (15.2) | |
| Hypertension | No | 10 (58.8) | 13 (43.3) | 22 (47.8) | 0.307[c] |
| | Yes | 7 (41.2) | 17 (56.7) | 24 (52.2) | |
| Coronary artery disease | No | 12 (70.6) | 21 (70.0) | 33 (70.2) | 0.966[c] |
| | Yes | 5 (29.4) | 9 (30.0) | 14 (29.8) | |
| Creatinine at diagnosis (mg/dL) | | 3.1 (1.3-8.2) | 2.5 (1.3-8.9) | 2.8 (1.3-8.9) | 0.406[d] |
| Glomerular Filtration Rate at Diagnosis (mL/min/1.73 $m^2$) | | 21 (8-41) | 23 (5-56) | 21 (5-56) | 0.308[d] |
| Urea at Diagnosis (mg/dL) | | 49 (21-93) | 39 (14-95) | 42 (14-95) | 0.203[d] |
| Free Light Chain Kappa/Lambda Ratio | | 1.14 (0-94) | 3.51 (0-1466.00) | 2.60 (0-1466.00) | 0.458[d] |
| Proteinuria (mg/24h) | | 4950 (400-17000) | 2200 (209-20000) | 3400 (209-20000) | 0.270[d] |
| Albuminuria (mg/24h) | | 98 (24-2000) | 120 (10-10000) | 112 (10-10000) | 0.831[d] |
| Hypercalcemia | No | 11 (64.7) | 18 (60.0) | 29 (61.7) | 0.750[c] |
| | Yes | 6 (35.3) | 12 (40.0) | 18 (38.3) | |
| Acute Kidney Injury Staging | | | | | 0.168[d] |
| | Stage 1 | 4 (23.5) | 12 (40.0) | 16 (34.0) | |
| | Stage 2 | 2 (11.8) | 5 (16.7) | 7 (14.9) | |
| | Stage 3 | 11 (64.7) | 13 (43.3) | 24 (51.1) | |
| Number of Plasma Exchanges | | 2 (1-5) | N/A | 2 (1-5) | N/A |
| Dialysis | Not Performed | 11 (64.7) | 24 (80.0) | 35 (74.5) | 0.306[b] |
| | Performed | 6 (35.3) | 6 (20.0) | 12 (25.5) | |
| Chemotherapy Regimens | | | | | 0.228[b] |
| Bortezomib-based | | 16 (94.1) | 23 (76.7) | 39 (83.0) | |
| Others | | 1 (5.9) | 7 (23.3) | 8 (17.0) | |

*[a] Independent Samples t-Test, [b] Fisher's Exact Test, [c] Pearson's Chi-Square Test, [d] Mann-Whitney U Test*

*Bortezomib-based regimens (Vel-Dex: Bortezomib, Dexamethasone; VCD: Bortezomib, Cyclophosphamide, Dexamethasone) and Others, including Lenalidomide-based regimens (VRD: Bortezomib, Lenalidomide, Dexamethasone) and Daratumumab-based regimens (Dara-VCD: Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone; Dara-VRD: Daratumumab, Bortezomib, Lenalidomide, Dexamethasone).*

Similarly, in the Non-PE Group (n= 30), no significant changes in treatment response distributions were observed between the first and second chemotherapy cycles. The Related-Samples McNemar Change Test retained the null hypothesis, confirming consistent response distributions over time (p= 0.500) (Figure 1B). These results demonstrate that treatment response dynamics in both groups remained stable during the early treatment cycles, with no apparent benefit of TPE observed in this analysis.

### *Creatinine Dynamics Across Clinical Parameters*

In the PE group, creatinine dynamics—defined as the change from baseline to post-therapy levels—showed no statistically significant variation across key clinical parameters. These parameters included albuminuria, proteinuria, oliguria, dialysis status, and AKI severity during the first and second cycles of chemotherapy.

**Table 2.** Impact of plasma exchange on renal function and involved immunoglobulin levels

| Variables | Pre-Plasma Exchange Median (min-max) | Post-Plasma Exchange Median (min-max) | Change (Δ) | p-value |
|---|---|---|---|---|
| Creatinine (mg/dL) | 3.1 (1.3-8.2) | 2.6 (0.9-7) | -0.5 | 0.002[a] |
| Involved Heavy Chain Levels (mg/dL) | 3900 (656-10000) | 941 (11.3-6460) | -2959 | 0.013[a] |
| Involved Free Light Chain Levels (mg/dL) | 415 (46.9-18000) | 213 (4.5-3720) | -202 | 0.009[a] |

[a] *Wilcoxon Signed-Rank Test. The change (Δ) indicates the median difference between pre- and post-plasma exchange measurements.*

Creatinine dynamics were further evaluated according to relevant clinical parameters. When patients were stratified by albuminuria status (>300 mg/24h vs. ≤ 300 mg/24h), no significant differences were observed in either the first (p=0.316) or second (p=0.599) treatment cycles. A similar pattern was noted for proteinuria, where patients with proteinuria >3000 mg/24h showed comparable creatinine changes to those with ≤ 3000 mg/24h, with p-values of 0.428 and 0.147 for the first and second cycles, respectively. The presence of oliguria was likewise not associated with distinct creatinine dynamics, as indicated by non-significant results in both cycles (p= 0.918 and p= 0.758). Dialysis requirement also did not lead to differential changes; creatinine dynamics were similar between patients who underwent dialysis and those who did not (p= 0.808 and p= 0.525). Finally, subgroup analysis by AKI severity (Stages 1-3) showed no meaningful variation, with p-values of 0.280 and 0.267 across the two cycles. Collectively, these findings indicate that albuminuria, proteinuria, oliguria, dialysis status, and AKI severity did not exert a significant impact on creatinine dynamics during the early phases of treatment.

### *Assessment of Chemotherapy Cycles on Renal Function*

Creatinine levels significantly decreased over time in both the PE and Non-PE groups from baseline to the second chemotherapy cycle (p< 0.001 for both). In the PE group, creatinine levels declined from a median of 3.1 mg/dL (range: 1.3-8.2) at baseline to 2.1 mg/dL (range: 0.5–6.0) after the first chemotherapy cycle and 1.7 mg/dL (range: 0.6-6.8) after the second chemotherapy cycle. Similarly, in the Non-PE group, levels decreased from 2.5 mg/dL (range: 1.3–8.9) at baseline to 1.8 mg/dL (range: 0.9–8.6) after the first chemotherapy cycle and 1.4 mg/dL (range: 0.9–7.4) after the second chemotherapy cycle. However, no significant differences in creatinine levels were observed between the groups at any time point (p= 0.406, p= 0.888, and p= 0.900 for baseline, first cycle, and second cycle, respectively) (Table 4).

**Table 3.** Correlation between plasma exchange frequency, renal function improvement, and changes in immunoglobulin dynamics

| Variables | | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| 1. Change in Serum Creatinine Levels (Δ Creatinine) | r | 1 | | | |
| | p[a] | | | | |
| 2. Change in Free Light Chain Levels (Δ Free Light Chains) | r | -0.030 | 1 | | |
| | p[a] | 0.934 | | | |
| 3. Change in Heavy Chain Levels (Δ Heavy Chains) | r | -0.200 | -0.115 | 1 | |
| | p[a] | 0.580 | 0.751 | | |
| 4. Number of Plasma Exchange Sessions | r | 0.795 | 0.318 | -0.331 | 1 |
| | p[a] | 0.006 | 0.371 | 0.351 | |

*r* Correlation Coefficient, [a] Spearman's Correlation Coefficient. Δ (Delta) represents the change in values calculated as the difference between baseline (pre-plasma exchange) and post-plasma exchange measurements for each parameter.

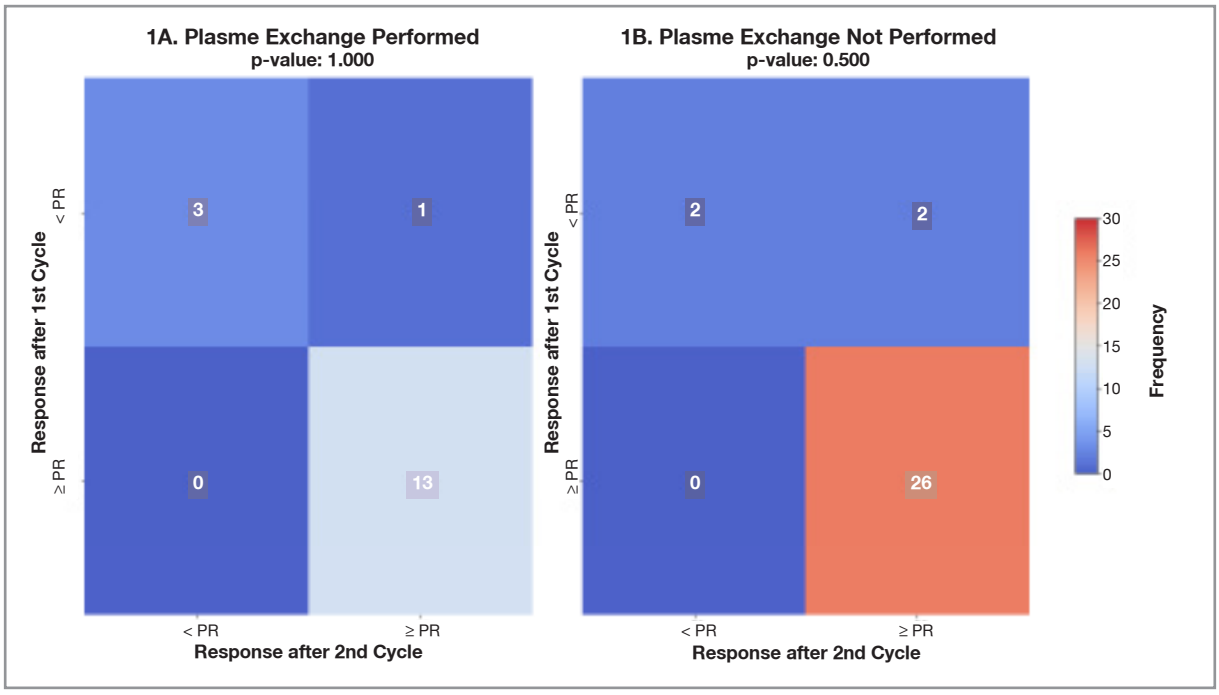


**Figure 1.** Comparison of treatment response dynamics between plasma exchange and non-plasma exchange groups across first and second chemotherapy cycles
**(A)** Improvement in treatment response distributions (≥PR and <PR) in the plasma exchange group,
**(B)** Stable treatment response distributions (≥PR and <PR) in the non-plasma exchange groupg

***PR:*** *Partial Response. Statistical Method: The McNemar test was used to evaluate pre- and post-treatment response changes for paired data.*

Furthermore, the impact of chemotherapy regimens on creatinine dynamics was analyzed in the overall cohort. As illustrated in Figure 2, bortezomib-based regimens led to a significantly greater reduction in serum creatinine levels after the first chemotherapy cycle compared to regimens incorporating novel agents (p= 0.021). However, this difference was no longer statistically significant following the second chemotherapy cycle (p= 0.091), suggesting that while bortezomib-based therapies may provide an early renal benefit, the effect equilibrates over subsequent treatment cycles.

## DISCUSSION

This study provides valuable insights into the role of early TPE in MM-associated AKI, particularly regarding renal recovery, dialysis independence, and treatment outcomes. While prior research has primarily focused on the efficacy of TPE[8], our findings contribute to the literature by assessing the real-world clinical impact of early TPE and contextualizing its role within the evolving framework of chemotherapy-driven renal recovery strategies.

TPE has historically been considered a supportive intervention for MM-induced AKI, aiming to rapidly reduce circulating FLC burden and prevent irreversible renal damage. The study by Dhakal, et al. reported a steady rise in TPE utilization from 1993 to 2015, yet its clinical benefits remain uncertain. While the proportion of MM hospitalizations involving TPE increased from 1% (1993-1999) to 2.1% (2008-2015), in-hospital mortality among TPE recipients declined significantly from 17.5% to 8.9%.[8] This decline likely reflects advancements in supportive care and novel anti-myeloma therapies, though the direct impact of TPE remains debated.

The largest randomized controlled trial on TPE in MM-associated AKI, conducted by Clark, et al., found no significant differences in OS between the TPE and control groups (33.3% vs. 32.8% mortality at six months). Additionally, dialysis independence at six months was comparable between groups (41.6% vs. 36.8%, p= 0.20), and the rates of new dialysis initiation post-treatment remained similar (20.9% vs. 20.0%). Although within-group im-

**Table 4.** Comparison of creatinine levels across treatment phases in plasma exchange and non-plasma exchange groups

| Group | Baseline Creatinine | Creatinine After Cycle 1 | Creatinine After Cycle 2 | p-value |
|---|---|---|---|---|
| Plasma Exchange | 3.1 (1.3-8.2) | 2.1 (0.5-6.0) | 1.7 (0.6-6.8) | < 0.001[a] |
| Non-Plasma Exchange | 2.5 (1.3-8.9) | 1.8 (0.9-8.6) | 1.4 (0.9-7.4) | < 0.001[a] |
| p-value (between groups) | 0.406[b] | 0.888[b] | 0.900[b] | N/A |

[a] *Friedman test,* [b] *Mann-Whitney U test*

provements in GFR were statistically significant, between-group differences were negligible.[10] Notably, this study had several limitations, including a renal biopsy performed in only one patient, a fixed number of TPE sessions (5-7), and the absence of serial FLC monitoring. Our study addresses these gaps by evaluating real-world patient outcomes while integrating chemotherapy response dynamics and personalized TPE protocols.

In our cohort, the number and frequency of TPE sessions were individualized according to daily renal and biochemical trends rather than a fixed protocol. This flexible, response-guided strategy allowed early discontinuation in patients showing prompt improvement and continuation in those with persistent FLC elevation or delayed creatinine recovery. Such an adaptive approach may partly explain the observed positive correlation between session count and creatinine improvement (r= 0.795, p= 0.006), emphasizing the clinical relevance of tailoring extracorporeal therapy to patient-specific kinetics. Interestingly, patients in the non-PE group exhibited slightly greater creatinine improvement despite similar baseline renal function. This finding may reflect the strong renal recovery potential of early bortezomib-based chemotherapy and the higher initial AKI severity among patients selected for TPE, both of which could have influenced response kinetics.

The International Myeloma Working Group recommends high-cutoff (HCO) hemodialysis with anti-myeloma therapy as the preferred approach for acute renal impairment due to cast nephropathy (grade B). However, if HCO-hemodialysis is unavailable, TPE may be beneficial in select patients with proven acute renal impairment or cases strongly suspected to be related to light chain cast nephropathy (grade C)[19], highlighting the importance of careful patient selection. Similarly, the American Society for Apheresis guidelines acknowledge TPE as a potential adjunctive therapy for myeloma CN, primarily for its role in rapidly reducing circulating FLC levels.[20]

The emergence of modern chemotherapy regimens has profoundly reshaped the approach to renal recovery in MM-associated AKI. Proteasome inhibitors (e.g., bortezomib) and monoclonal antibodies (e.g., daratumumab) have demonstrated superior efficacy in restoring renal function, prompting reconsideration of the necessity of TPE in the era of targeted MM therapies. Bachmann et al. highlighted that chemotherapy alone can drive significant renal recovery 11, reinforcing its central role as the primary therapeutic strategy. Likewise, Kuzume et al. demonstrated that daratumumab-based regimens rapidly reduce FLC levels[21], suggesting that adequate FLC clearance through targeted therapy may diminish the need for extracorporeal interventions such as TPE.

HCO dialysis has been explored as a potential extracorporeal strategy to enhance renal recovery in MM-associated AKI. By effectively reducing serum FLC concentrations, HCO dialysis may help mitigate tubular damage and cast formation.[22] A randomized clinical trial demonstrated that HCO dialysis was associated with higher dialysis independence rates compared to conventional dialysis at 12 months (60.9% vs. 37.5%, p= 0.02), with a statistically significant benefit observed from 6 months onward. However, no significant difference was found at 3 months, and further research is needed to confirm its long-term clinical impact.[23]

However, despite its potential benefits, HCO dialysis is not universally available, and concerns remain

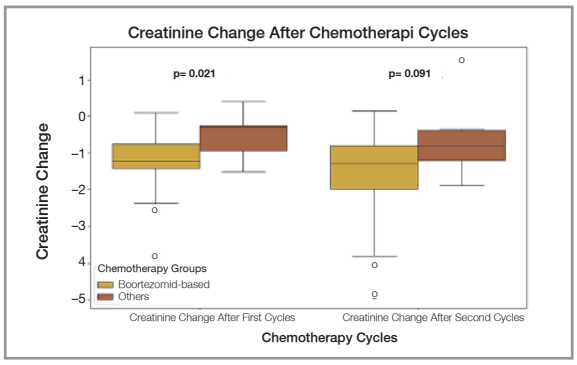


**Figure 2.** Creatinine Change Following Chemotherapy Cycles in Bortezomib-Based and Other Regimens

*Box plots illustrating the changes in serum creatinine levels after the first and second chemotherapy cycles in patients receiving Bortezomib-based regimens (Vel-Dex: Bortezomib, Dexamethasone; VCD: Bortezomib, Cyclophosphamide, Dexamethasone) and Others, including Lenalidomide-based regimens (VRD: Bortezomib, Lenalidomide, Dexamethasone) and Daratumumab-based regimens (Dara-VCD: Daratumumab, Bortezomib, Cyclophosphamide, Dexamethasone; Dara-VRD: Daratumumab, Bortezomib, Lenalidomide, Dexamethasone).*
*Creatinine dynamics were calculated as the difference between baseline and post-therapy levels. P-values from the Mann-Whitney U test represent statistical comparisons between groups.*

regarding hemodynamic instability, electrolyte imbalances, and treatment-associated complications. The EuLITE trial included comprehensive safety monitoring and reporting adverse events related to both dialysis and chemotherapy, though conclusive evidence on HCO dialysis-specific risks remains limited 24. Ongoing randomized controlled trials, including the MYRE and EuLITE studies[23,24], are evaluating its clinical efficacy compared to standard dialysis, with early findings suggesting a potential benefit in biopsy-confirmed cast nephropathy.

The primary limitation of this study is its retrospective design, which introduces potential selection bias. Additionally, the heterogeneity in chemotherapy regimens may have influenced renal outcomes, making it difficult to isolate the precise effects of early TPE. While long-term renal function was assessed, further studies with larger cohorts and standardized treatment protocols are needed to confirm these findings and establish more definitive clinical guidelines.

Future research should focus on prospective trials to determine the optimal sequencing of TPE, HCO dialysis, and chemotherapy in MM-associated AKI. Further investigations should explore whether daratumumab-based regimens can reduce the need for extracorporeal interventions. Additionally, developing personalized treatment algorithms incorporating biomarkers such as sFLC reduction rates could enhance patient selection and renal recovery strategies.

## Conclusion

This study underscores the potential role of early TPE in facilitating renal recovery in MM patients with AKI, particularly those with proven cast nephropathy and high FLC burden. However, chemotherapy remains the cornerstone of renal recovery, with proteasome inhibitors and anti-CD38 monoclonal antibodies playing central roles. While emerging strategies such as HCO dialysis and plasma-free plasmapheresis show promise in optimizing renal outcomes, their clinical integration requires further validation. Moving forward, well-designed prospective trials are essential to refine patient selection, treatment sequencing, and the long-term efficacy of TPE in the management of MM-associated AKI.

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