Supplement 2

Alternative Net Ultrafiltration Rate Strategies in Acute Kidney Injury: A Feasibility Randomized Clinical Trial

Raghavan Murugan, Victor Talisa, Chung-Chou H. Chang, Nasrin Nikravangolsefid, Waryaam Singh, Brad Butcher, Ali Al-Khafaji, Scott Gunn, Firas Abdulmajeed, Phillip Lamberty, David Huang, Paul M. Palevsky, Kianoush Kashani

for the

Restrictive versus Liberal Rate of Extracorporeal Volume Removal Evaluation in Acute Kidney Injury (RELIEVE-AKI) Study Investigators

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The RELIEVE-AKI Study Investigators

Pittsburgh Clinical Center: UPMC Presbyterian Hospital – Raghavan Murugan*, Paul Palevsky, David T. Huang, Ali Al-Khafaji, Scott Gunn, Philip Lamberty, Michele Elder, Maham Raza, Denise Scholl, Tina Vita, William Sabol, Dan Ricketts, Thomas Mathie, Linda Stevanus-Schmadel, Anna Woodall, Mashiyat Ahmed. UPMC Mercy Hospital – Brad Butcher, Jonathan Bishop, Firas Abdulmajeed.

Mayo Clinic: Mayo Clinic Methodist Campus – Kianoush Kashani*, Justin Patri, Nasrin Nikravangolsefid, Waaryam Singh, Andrea Katah, Supawadee Supadungsuk, Tom Sanger. Mayo Clinic St. Marys Campus – Kianoush Kashani

Clinical Coordinating Center: Raghavan Murugan, Kianoush Kashani, Paul Palevsky, Chung-Chou H. Chang, Victor B. Talisa, Michele, Elder.

Data and Safety Monitoring Board: Kathleen Liu, Ashita Tolwani, Manisha Jhamb, Dana Fuhrman, Hsing-Hua Sylvia Lin, Susan Sandusky, Sammy Massimino

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Ivonne Schulman (Program Official)

* Clinical Center Lead Principal Investigator

eMethods 1: Study Procedures

Study Design and Setting

Participants were enrolled from 5 ICUs at the University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania, and 5 ICUs at the Mayo Clinic in Rochester, Minnesota. The study protocol adhered to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist [1, 2]. A 5-member data and safety monitoring board (DSMB) reviewed the trial approximately every 6 months and had the authority to recommend trial cessation for safety concerns. The study commenced on July 5th, 2022, and enrollment was stopped on June 17th, 2024, due to funding constraints after enrolling 99 patients. The first patient was enrolled on July 14th, 2022, and the last on May 31st, 2024.

Study Population and Clinical Equipoise

Provisionally, eligibility required meeting all inclusion criteria and none of the exclusion criteria. Once eligible, we assessed clinical equipoise regarding the UF_{NET} rate by asking the attending intensivist or nephrologist twice daily whether they strongly believed that emergent, rapid net fluid removal should be performed or deferred. If the answers to both questions were negative, the patient was fully eligible, and efforts to obtain informed consent began. If the attending physician did not have equipoise, the study team reapproached them within 12-24 hours to reassess their equipoise. Patients or their surrogates were approached only if the attending had equipoise, and after written informed consent was obtained, the patient was considered enrolled in the trial.

Randomization

In this stepped-wedge trial lasting 23 months and 12 days, patients in all ICUs were assigned to the liberal group for the first 6 months. Thereafter, patients in a single ICU were assigned to the restrictive group randomly every 2 months. The statistician used a computer-generated randomization to determine when each ICU would transition from the liberal to the restrictive group. One month before patient recruitment began at each ICU, we prepared standardized education materials and conducted study orientation for ICU clinicians [3]. Blinding healthcare providers was not feasible due to the nature of the study interventions.

Study Intervention

We followed standard start-up procedures, initiating the intervention within 24 hours of study enrollment. To precisely calculate the UF_{NET} rate, we used a web-based UF_{NET} rate calculator that estimated the hourly UF_{NET} rate range to be set on the CKRT

machine, based on the intervention group allocation, the rate of intravenous fluids infused in the current hour, and the patient's predicted body weight (PBW). We accounted for the rate of intravenous infusions because the UF_{NET} rate dosing in our study represented the net intravascular volume removed beyond the volume infused in the current hour, and not just the hourly machine-set fluid removal rate. We chose predicted PBW because it is free of confounding by fluid overload and catabolism due to critical illness, as well as measurement errors [4, 5]. In both groups, the initial UF_{NET} rate was set at 0.5 mL/kg/h and then increased by 0.5 mL/kg/h, as tolerated (eFigure 3) [3]. In the restrictive group, the UF_{NET} rate was titrated up to 0.5-1.5 mL/kg/h and maintained throughout the study. In the liberal group, the UF_{NET} rate was titrated to 2.0-5.0 mL/kg/h and maintained. The protocol permitted interruption of net fluid removal due to patient instability, at the clinical team's discretion. Following any interruption in either group, net fluid removal was reinitiated at 0.5 mL/kg/h and then titrated according to the treatment group as described above.

Concomitant Care

We provided clinicians with guidelines for the assessment and management of hemodynamic instability, recommended conservative fluid management, and outlined criteria for rescue UF_{NET} procedures for fluid overload. Management of CKRT, including the prescription of modality, blood flow, dialysate, replacement fluids, hemofilter, and anticoagulation, was determined by the attending nephrologist. The study protocol was continued until the attending physician determined that CKRT was no longer needed, a decision was made to transition the patient to intermittent hemodialysis, the patient or surrogate decision-makers decided to withdraw life-sustaining treatment, the patient died, or day 28 after study enrollment, whichever occurred first.

Outcomes

The three coprimary feasibility endpoints were the between-group difference in mean delivered UF_{NET} rate, protocol adherence, and recruitment rate. The primary objective was to achieve a minimum of 0.53 mL/kg/h separation in the patient-delivered mean UF_{NET} rates between the restrictive and liberal UF_{NET} rate groups. We defined protocol deviation a priori as a delivered UF_{NET} rate that lies >0.5 mL/kg/h outside of the target UF_{NET} rate range in the assigned treatment group for greater than six consecutive hours during fluid removal without significant changes in mean arterial pressure (MAP <65 mmHg or <90 mmHg)[3]. As such, out-of-range UF_{NET} rates >0.5 mL/kg/h beyond the target UF_{NET} rate range did not constitute a protocol deviation when the bedside team titrated the UF_{NET} rate as required to manage the patient's hemodynamics. A successful recruitment rate was defined as enrolling one patient every 2 months per ICU during the trial. Secondary endpoints included daily and cumulative fluid balance, duration of KRT and mechanical ventilation, organ-failure free days, ICU and hospital length of stay, hospital mortality, and KRT dependence at hospital discharge. A detailed description of safety endpoints is provided in eTable 2.

Statistical Analysis

A detailed description of the sample size was previously reported [3]. Briefly, we initially estimated the sample size at 144 patients, with 1 of the 6 ICUs transitioning from the liberal to the restrictive group at each of 6 steps, every 3 months. However, due to a slower-than-expected enrolment rate, the sample size was reduced to 112 patients (56 per group), and the number of ICUs increased to 10 after enrollment of 9 patients on December 13, 2022. Assuming that each of the 10 ICUs enrolled a minimum of 0.93 patients per 2 months over 24 months across 12 time periods, we estimated that 111 patients would have 80% power at a two-sided alpha of 0.05 to reject the null hypothesis that the average UF_{NET} rate was at least 0.53-0.57 mL/kg/h different between the two groups, using intra-cluster correlation coefficient of 0.01, at a SD of 0.75, and assuming mean UF_{NET} rate of 1.0 mL/kg/h [3]. The DSMB and the Human Research Protection Office approved the revised sample-size calculations, and a statistical analysis plan was prepared following the second DSMB meeting.

All analyses were performed on an intention-to-treat basis, with no interim analyses. We also performed exploratory per-protocol analyses in which the assigned intervention was adhered to. We fitted linear mixed model (LMM) to test the null hypothesis that the mean difference in the patient-averaged delivered UF_{NET} rate was less than 0.53 mL/kg/h after adjusting for prespecified variables (age, baseline estimated glomerular filtration rate (eGFR), acute physiology and chronic health evaluation [APACHE]-III scores, Elixhauser comorbidity index score, mechanical ventilation, admission source, percentage of fluid overload, sepsis, and cardiovascular sequential organ failure assessment [SOFA] score and accounting for temporal and clustering effects [6-8]. In this model, ICU was included as a random intercept to account for within-cluster correlation, and time was modeled by study period to account for secular trends inherent to the stepped-wedge design. Given the feasibility trial and the limited number of participants per cluster-period, the model was specified parsimoniously to promote stability and convergence.

We conducted prespecified exploratory analysis to examine between-group differences in peak UF_{NET} and longitudinal UF_{NET} rate trajectories. Prespecified subgroup analysis was conducted among those with ≥10% fluid overload; eGFR ≥60mL/min/1.73m^2; UF_{NET} duration ≥6 before enrollment; age ≥65; presence of sepsis; and baseline cardiovascular SOFA score ≥3. For protocol adherence, we report the number of deviations per UF_{NET} day, the number of days with UF_{NET} out of range for at least 6 consecutive hours, and the number of patients with at least 1 occurrence of the UF_{NET} rate out of range for 6 consecutive hours. Protocol deviations, secondary outcomes, and safety outcomes were compared using generalized LMM regression with appropriate link functions. The recruitment rate was calculated as the mean (SD) number of patients recruited per ICU per two months. Analysis was performed in R (version 4.1.3) with a significance level of $P<0.05$.

eTable 1: CONSORT Checklist

Section/topic	No	CONSORT 2025 checklist item description	Reported on page no.
Title and abstract			
Title and structured abstract	1a	Identification as a randomised trial	1
	1b	Structured summary of the trial design, methods, results, and conclusions	3
Open science			
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	5
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	5,6
Data sharing	4	Where and how the individual de-identified participant data (including data dictionary), statistical code and any other materials can be accessed	14
Funding and conflicts of interest	5a	Sources of funding and other support (eg, supply of drugs), and role of funders in the design, conduct, analysis and reporting of the trial	13
	5b	Financial and other conflicts of interest of the manuscript authors	13
Introduction			
Background and rationale	6	Scientific background and rationale	4
Objectives	7	Specific objectives related to benefits and harms	4
Methods			
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	14
Trial design	9	Description of trial design including type of trial (eg, parallel group, crossover), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5, Supplements 1,2
Changes to trial protocol	10	Important changes to the trial after it commenced including any outcomes or analyses that were not prespecified, with reason	Supplement 2
Trial setting	11	Settings (eg, community, hospital) and locations (eg, countries, sites) where the trial was conducted	5
Eligibility criteria	12a	Eligibility criteria for participants	5, Supplements 1, 2
	12b	If applicable, eligibility criteria for sites and for individuals delivering the interventions (eg, surgeons, physiotherapists)	5, Supplements 1, 2

Section/topic	No	CONSORT 2025 checklist item description	Reported on page no.
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication. If relevant, where additional materials describing the intervention and comparator (eg, intervention manual) can be accessed	5 and 6; see protocol; BMJO publication
Outcomes	14	Prespecified primary and secondary outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome	6, Supplements 1,2
Harms	15	How harms were defined and assessed (eg, systematically, non-systematically)	6, Supplements 1, 2
Sample size	16a	How sample size was determined, including all assumptions supporting the sample size calculation	Supplements 1, 2
	16b	Explanation of any interim analyses and stopping guidelines	Supplement 3
Randomisation:			
Sequence generation	17a	Who generated the random allocation sequence and the method used	Supplement 2
	17b	Type of randomisation and details of any restriction (eg, stratification, blocking and block size)	Supplement 2
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence (eg, central computer/telephone; sequentially numbered, opaque, sealed containers), describing any steps to conceal the sequence until interventions were assigned	Supplement 2
Implementation	19	Whether the personnel who enrolled and those who assigned participants to the interventions had access to the random allocation sequence	Supplement 2
Blinding	20a	Who was blinded after assignment to interventions (eg, participants, care providers, outcome assessors, data analysts)	Supplement 2
	20b	If blinded, how blinding was achieved and description of the similarity of interventions	Supplement 2
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes, including harms	Supplements 2,3
	21b	Definition of who is included in each analysis (eg, all randomised participants), and in which group	Supplements 2,3
	21c	How missing data were handled in the analysis	Supplement 3
	21d	Methods for any additional analyses (eg, subgroup and sensitivity analyses), distinguishing prespecified from post hoc	Supplements 2,3
Results			
Participant flow, including flow diagram	22a	For each group, the numbers of participants who were randomly assigned, received intended intervention, and were analysed for the primary outcome	7, Supplement 2

Section/topic	No	CONSORT 2025 checklist item description	Reported on page no.
Recruitment	22b	For each group, losses and exclusions after randomisation, together with reasons	7, Supplement 2
	23a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	7, Supplement 2
	23b	If relevant, why the trial ended or was stopped	7, Supplement 2
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered (eg, where appropriate, who delivered the intervention/comparator, how participants adhered, whether they were delivered as intended (fidelity))	7
	24b	Concomitant care received during the trial for each group	7
Baseline data	25	A table showing baseline demographic and clinical characteristics for each group	Supplement 2
Numbers analysed, outcomes and estimation	26	For each primary and secondary outcome, by group: ● the number of participants included in the analysis ● the number of participants with available data at the outcome time point ● result for each group, and the estimated effect size and its precision (such as 95% confidence interval) ● for binary outcomes, presentation of both absolute and relative effect size	Supplement 2
Harms	27	All harms or unintended events in each group	Supplement 2
Ancillary analyses	28	Any other analyses performed, including subgroup and sensitivity analyses, distinguishing pre-specified from post hoc	Supplement 2
Discussion			
Interpretation	29	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Supplement 2
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability, and, if relevant, multiplicity of analyses	11

Citation: Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025; 388:e081123. https://dx.doi.org/10.1136/bmj-2024-081123

*We strongly recommend reading this statement in conjunction with the CONSORT 2025 Explanation and Elaboration and/or the CONSORT 2025 Expanded Checklist for important clarifications on all the items. We also recommend reading relevant CONSORT extensions. See www.consort-spirit.org.

eTable 2: Description of Outcomes and Measures

Outcome	Measure Definition
Delivered Net Ultrafiltration (UF_{NET}) rate	The delivered UF_{NET} rate variable is defined as net intravascular fluid removal rate from the patient after accounting for intravenous fluids infused in the current hour and adjusted for predicted body weight. The overall mean delivered UF_{NET} rate for each hour will be calculated from all patients enrolled in the restrictive and liberal groups.
Protocol deviation	A delivered UF_{NET} rate that lies >0.5 mL/kg/h outside of the target UF_{NET} rate range in the assigned treatment group for greater than six consecutive hours during fluid removal without significant changes in mean arterial pressure (*i.e.,* mean arterial pressure [MAP] <65 mmHg or systolic blood pressure (SBP) ≥90 mmHg). As such, out-of-range UF_{NET} rates >0.5 mL/kg/h beyond the target UF_{NET} rate range will not constitute a protocol deviation when the bedside team titrated the UF_{NET} rate as required to manage the patient hemodynamics (*i.e.,* when clinicians appropriately decreased the rate or stopped fluid removal for hypotension; increased the rate for hypertension or treatment of respiratory distress due to pulmonary edema).
Recruitment rate	No. of patients or their legally authorized representative who provided written informed consent for trial participation per month per center.
Toleration of UF_{NET}	Toleration of UF_{NET} will be defined as the absence of hemodynamic instability following initiation of UF_{NET} since there are no clinically validated tolerance parameters. We have chosen this construct for tolerance because in current clinical practice, tolerance to UF_{NET} is based on maintaining hemodynamic stability using MAP, SBP and, heart rate.
Hemodynamic instability	Hemodynamic instability during UF_{NET} will be defined as a new MAP <65 mmHg, SBP <90mmHg or a decline in SBP >40 mmHg, and/or a >30% increase in dose of existing vasopressors, initiating a new vasopressor, administration of fluid bolus with a goal to maintain MAP ≥65 mmHg, SBP ≥90mmHg or discontinuation of fluid removal during continuous kidney replacement therapy. The reason for choosing increased need of vasopressors, fluid bolus or discontinuation of fluid removal is to account for clinically significant hypotension that required an intervention.
Hospital Mortality	Death prior to discharge alive from study hospital will be counted as hospital mortality. Patients whose final status is unknown but who are known to be alive on study day 28 based on known event dates will be counted as alive.
Kidney replacement therapy dependence	Patients receiving any form of kidney replacement therapy 72 hours before discharged alive will be considered dialysis dependent. If a patient dies before day 28, the patient will be considered dialysis dependent. Patients who are not dialysis dependent by day 28 but continue to remain in the hospital or receive dialysis after day 28 will be considered liberated from dialysis.
Organ failure free days	Organ failure is defined as present on any date when the most abnormal vital signs or clinically available lab value meets the definition of clinically significant organ failure according to sequential organ failure assessment (SOFA) scores. Patients will be followed for development of organ failures to death, hospital discharge or study day 28, whichever comes first. Each day a patient is alive and free of a given organ failure will be scored as a failure-free

Outcome	Measure Definition
	day. Any day that a patient is alive and free of all organ failures will represent days alive and free of all organ failure.
Intradialytic hypotension	Intradialytic hypotension will be defined as a new MAP <65 mmHg, SBP<90mmHg or a decline in SBP >40 mmHg, and/or a >30% increase in dose of existing vasopressors, initiating a new vasopressor, or administration of fluid bolus with a goal to maintain (MAP) ≥ 65 mmHg, systolic blood pressure (SBP) ≥ 90mmHg.
Intradialytic hypertension	Intradialytic hypertension will be defined as new onset SBP ≥160 mmHg or MAP ≥80 mmHg for more than 1 hour in the absence of any vasopressor or inotrope use.
Intradialytic cardiac arrhythmias	Intradialytic new onset cardiac arrhythmias including supraventricular tachycardia, bradycardia, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, asystole/pulseless electrical activity will be diagnosed as per American Heart Association.
Rescue net ultrafiltration	Emergent use of rescue UF_{NET} with rates higher than the assigned treatment arm for more than 3 consecutive hours.
Severe hypokalemia	Severe hypokalemia is defined as a intradialytic potassium level <3.0 mg/dL. Severe hypocalcemia will be defined as intradialytic serum calcium level <1.90 mg/dL or ionized calcium <0.90 mmol/L.
Severe hypophosphatemia	Severe hypophosphatemia will be defined as intradialytic phosphate level <0.5 mg/dL.
Severe hypocalcemia	Severe hypocalcemia will be defined as intradialytic serum calcium level <1.90 mg/dL or ionized calcium <0.90 mmol/L.
Inability to close post-operative surgical wound due to edema	This will be determined as per the primary surgical service. Abdominal wounds left open for a second look or for abdominal re-exploration should not be counted unless there is concurrent tissue edema precluding abdominal closure.
New organ dysfunction due to fluid overload	New and worsening organ dysfunction will be assessed based on SOFA scoring. For instance, a patient with CV SOFA score of 3 at study initiation and now has score of 4 will be counted as worsening CV dysfunction. We will also capture new diastolic/systolic dysfunction on echocardiogram, pulmonary edema on chest X ray/CT scan, ileus on abdominal X ray/CT scan, bowel ischemia and anastomotic breakdown on CT scan/OR, transaminitis or hyperbilirubinemia; delirium using delirium scores on medical records, poor wound healing, wound infection, and pressure ulceration per nursing records, new onset arterial and venous thrombosis as documented by imaging and clinical examination, and anemia, hemolysis and thrombocytopenia as documented in the laboratory studies.
Severe anemia	Anemia requiring red cell transfusion.
Severe thrombocytopenia	Thrombocytopenia requiring platelet transfusion.
Secondary infections	New onset secondary infections occurring after initiation of study intervention will be collected based on culture data, antibiotic use and suspected sepsis as per clinician judgment

eTable 3: Characteristics of Study ICUs

Study ICU	Hospital	ICU type	Location	No. of beds	No. enrolled (Liberal)	No. enrolled (Restrictive)	Total enrolled
1	UPMC Presbyterian	Transplant	Pittsburgh, PA	12	6	4	10
2	UPMC Presbyterian	Surgical Trauma	Pittsburgh, PA	22	3	0	3
3	UPMC Presbyterian	Medical	Pittsburgh, PA	32	11	1	12
4	UPMC Mercy	Medical - Surgical	Pittsburgh, PA	20	1	3	4
5	UPMC Mercy	Neurology/ Neurosurgery/ Medical	Pittsburgh, PA	18	3	0	3
6	Mayo Clinic Methodist	Medical-Surgical	Rochester, MN	21	7	7	14
7	Mayo Clinic St. Marys	Medical	Rochester, MN	32	13	3	16
8	Mayo Clinic St. Marys	Cardiac	Rochester, MN	18	2	7	9
9	Mayo Clinic St. Marys	CV surgery	Rochester, MN	32	4	15	19
10	Mayo Clinic St. Marys	Surgical	Rochester, MN	18	6	3	9

eTable 4: No. of Eligible and Enrolled Patients

Step	No. screened	No. eligible	No. enrolled	No. screened	No. eligible	No. enrolled
	UPMC			Mayo		
Step 1	1692	19	5	1379	20	6
Step 2	850	8	2	886	12	6
Step 3	854	7	5	822	17	10
Step 4	1257	11	6	744	15	8
Step 5	1162	12	3	833	17	6
Step 6	791	9	2	693	13	8
Step 7	1090	9	2	863	17	8
Step 8	1052	10	1	800	18	8
Step 9	1154	12	3	720	19	6
Step 10	675	9	3	528	9	1
Total	**10,577**	**106**	**32**	**8,268**	**157**	**67**

eTable 5: Patient Characteristics at Trial Enrolment by Study Period

Variable	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8	Step 9	Step 10
No. of participants	11	8	15	14	9	10	10	9	9	4
Fluid overload percent, median (IQR)	2.75 (0.38-28.36)	5.21 (3.41-8.49)	6.84 (1.01-13.57)	10.12 (5.75-18.52)	1.46 (-3.75-6.58)	7.34 (1.02-18.12)	5.11 (2.48-11.02)	14.11 (5.20-15.82)	3.98 (-5.86-5.49)	5.76 (1.14-22.85)
Cardiovascular SOFA score, median (IQR)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	3 (1-4)	3 (2-3)	3 (3-3)	3 (3-3)	3 (1.5-3.5)
Vasopressor support, No. (%)	9 (81.8)	5 (62.5)	12 (80.0)	9 (64.3)	6 (66.6)	2 (20.0)	6 (60.0)	6 (66.6)	4 (44.4)	4 (4.04)
APACHE-III score, median (IQR)	88 (71-99)	88.5 (71.5-107)	95 (80-101)	84 (74-91)	79 (63-92)	81 (71-94)	77 (63-84)	79 (70-89)	96 (77-100)	94 (73-108.5)
Mechanical Ventilation, No. (%)	6 (54.5)	7 (87.5)	11 (73.3)	9 (64.3)	6 (66.6)	4 (40.0)	4 (40.0)	5 (55.6)	5 (55.5)	3 (75.0)
Ultrafiltration rate, mL/hour, median (IQR)	100 (50-180)	75 (50-120)	50 (45-125)	50 (50-100)	100 (100-200)	50 (50-110)	250 (100-400)	150 (60-200)	25 (0-50)	75 (50-125)

eTable 6: Baseline Characteristics of Patients at Study Enrolment

Characteristics	No. (%)		
	All (n=97)	**Liberal (N= 55)**	**Restrictive (N=42)**
Age, years, median (IQR)	59.0 (46.0-70.0)	59.0 (40.0-69.0)	62.0 (49.0-71.0)
Female sex	39 (40.2)	24 (43.6)	15 (35.7)
Ethnicity			
White	88 (90.7)	50 (90.9)	38 (90.5)
Black	6 (6.2)	3 (5.5)	3 (7.1)
Other	1 (1.0)	1 (1.8)	0 (0.0)
Prefer not to answer/Unknown	2 (2.1)	1 (1.8)	1 (2.4)
Actual body weight at hospital admission, kilograms, median (IQR)	83.3 (76.0-102.0)	83.3 (76.0-102.0)	83.3 (76.0-94.7)
Baseline serum creatinine, mg/dL, median (IQR)	1.0 (0.8-1.4)	1.0 (0.8-1.5)	1.0 (0.8-1.5)
Estimated glomerular filtration rate, mL/min/1.73m^2 median (IQR)[a]	84.0 (59.0-109.0)	81.0 (54.0-111.0	86.0 (64.0-108.0)
Elixhauser Comorbidity Index score[b]	13.0 (0.0-20.0)	11.0 (-1.0-20.0)	15.0 (4.0-28.0)
Pre-existing conditions			
Hypertension	58 (61.1)	31 (57.4)	27 (65.9)
Diabetes mellitus	32 (33.7)	19 (35.8)	13 (31.0)
Chronic kidney disease	45 (48.9)	20 (38.5)	25 (62.5)
Coronary artery disease	22 (23.7)	12 (22.6)	10 (25.0)
Heart failure	42 (46.2)	20 (39.2)	22 (55.0)
Liver disease	36 (38.7)	21 (41.2)	15 (35.7)
Metastatic cancer	8 (8.8)	6 (11.5)	2 (5.1)
Chronic pulmonary disease	38 (40.4)	16 (29.6)	22 (55.0)
Primary diagnosis			
Cardiovascular	37 (39.4)	17 (32.1)	20 (48.8)
Pulmonary	5 (5.3)	4 (7.5)	1 (2.4)
Gastrointestinal	26 (27.7)	15 (28.3)	11 (26.8)
Infection or sepsis	21 (22.3)	12 (22.6)	9 (22.0)
Neurologic	2 (2.1)	2 (3.8)	0 (0.0)
Oncologic	2 (2.1)	2 (3.8)	0 (0.0)
Other	1 (1.1)	1 (1.9)	0 (0.0)
Etiology of acute kidney injury			
Sepsis	48 (49.5)	28 (50.9)	20 (47.6)
Ischemic	75 (77.3)	38 (69.1)	37 (88.1)

Characteristics	No. (%)		
	All (n=97)	**Liberal (N= 55)**	**Restrictive (N=42)**
Nephrotoxic	18 (18.6)	9 (16.4)	9 (21.4)
Multifactorial	72 (74.2)	37 (67.3)	35 (83.3)
Risk factors for fluid overload in the past week			
Sepsis	53 (54.6)	31 (56.4)	22 (52.4)
Hemorrhage	29 (30.5)	18 (33.3)	11 (26.8)
Acute pancreatitis	5 (5.3)	4 (7.4)	1 (2.4)
Other	57 (60.0)	28 (51.9)	29 (70.7)
Source of admission			
Home	62 (74.7)	37 (72.5)	25 (78.1)
Skilled Nursing Facility	2 (2.4)	2 (3.9)	0 (0.0)
Assisted Living Facility	0 (0.0)	0 (0.0)	0 (0.0)
Other	17 (20.5)	10 (19.6)	7 (21.9)
Admission category			
Medical	64 (66.7)	41 (74.5)	23 (56.1)
Scheduled surgery	15 (15.5)	11 (20.0)	4 (9.5)
Emergency surgery	27 (27.8)	7 (12.7)	20 (47.6)
No. of days from ICU admission to study enrollment, days, median (IQR)	4.3 (2.3-9.7)	4.3 (2.0-8.6)	4.3 (2.6-13.8)
Clinical condition at study enrollment			
Sepsis	53 (54.6)	31 (56.4)	22 (52.4)
APACHE-III score, median (IQR)[c]	84.0 (71.0-98.0)	84.0 (70.0-98.0)	84.0 (71.0-100.0)
Cardiovascular SOFA score, median (IQR)[d]	3.0 (3.0-4.0)	3.0 (3.0-4.0)	3.0 (3.0-3.0)
Vasopressor support	63 (81.8)	38 (86.4)	25 (75.8)
Mechanical ventilation	60 (61.9)	34 (61.8)	26 (61.9)
Fluid overload percentage, median (IQR)	6.4 (1.4-14.1)	5.8 (1.0-17.1)	6.9 (3.0-12.8)
Cumulative fluid balance at enrollment, mL, median (IQR)	5,511.0 (1,345.9-10,870.9)	4,464.2 (910.2-13,582.0)	6,327.8 (3041.0-9,263.8)
Duration of fluid removal before enrollment, hrs	0.0 (0.0-19.0)	5.0 (0.0-31.0)	0.0 (0.0-10.0)
Oliguria/anuria	87 (89.7)	48 (87.3)	39 (92.9)
Urinary output, mL/24 hours, median (IQR)	80.0 (25.0-267.0)	80.0 (48.0-267.0)	92.5 (0.0-275.0)
Diuretic use	20 (21.5)	11 (20.8)	9 (22.5)

Characteristics	No. (%)		
	All (n=97)	**Liberal (N= 55)**	**Restrictive (N=42)**
Corticosteroid use	45 (48.4)	22 (41.5)	23 (57.5)
CKRT characteristics			
CVVH	61 (65.6)	28 (53.8)	33 (80.5)
CVVHD	6 (6.5)	3 (5.8)	3 (7.3)
CVVHDF	25 (26.9)	20 (38.5)	5 (12.2)
SCUF	1 (1.1)	1 (1.9)	0 (0.0)
Blood flow, mL/min, median (IQR)	200.0 (200.0-250.0)	250.0 (200.0-250.0)	200.0 (200.0-200.0)
Dialysate/Replacement flow, mL/h, median (IQR)	2,400.0 (2,000.0-2,775.0)	2,400.0 (2,000.0-2,700.0)	2,400.0 (2,000.0-3,000.0)
Ultrafiltration rate, mL/hour, median (IQR)	100.0 (50.0-150.0)	100.0 (50.0-150.0)	50.0 (50.0-150.0)
Anticoagulation use	62 (66.7)	29 (55.8)	33 (80.5)

IQR, interquartile range; ICU, intensive care unit; APACHE, acute physiology, and chronic health evaluation; SOFA, sequential organ failure assessment; CKRT, continuous kidney replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; SCUF, slow continuous ultrafiltration.

Data are presented as median (interquartile range [IQR]) or count N (percentage). No P values are provided as no formal statistical testing was conducted to compare baseline characteristics between groups, consistent with the feasibility trial design.

[a] Estimated using the race-free 2021 chronic kidney disease epidemiology equation [9].

[b] The Elixhauser Comorbidity Index score ranges from 0 to 29, with higher scores indicating more chronic coexisting conditions [10].

[c] The Acute Physiology and Chronic Health Evaluation (APACHE)-III score ranges from 0 to 299 with higher scores indicating greater severity of illness [11].

[d] The cardiovascular sequential organ failure assessment (SOFA) score ranges from 0 to 4 with higher scores indicating greater severity of cardiovascular dysfunction [12].

eTable 7: Pre-specified Subgroup Analysis

Subgroup	All	Liberal	Restrictive	P value	Adjusted P value*
Fluid overload					
≥10% (n=36)	1.75 (1.36-2.15)	1.94 (1.41-2.18)	1.73 (1.32-2.04)	0.152	0.964
<10% (n=61)	1.89 (1.36-2.48)	1.99 (1.54-2.75)	1.72 (1.22-2.14)	0.125**	0.168
eGFR, mL/min/1.73m^2					
≥60 (n=69)	1.74 (1.29-2.38)	1.89 (1.41-2.48)	1.62 (1.14-2.02)	0.123	0.976
<60 (n=28)	2.01 (1.59-2.87)	2.03 (1.79-2.73)	1.95 (1.41-3.01)	0.769	**
Fluid removal duration before enrollment, hours					
≥6 (n=38)	1.83 (1.32-2.33)	1.97 (1.45-2.62)	1.36 (0.88-1.77)	0.007**	0.059
<6 (n=59)	1.84 (1.38-2.53)	1.87 (1.33-2.67)	1.84 (1.38-2.53)	0.493	**
Age					
≥65 (n=38)	1.86 (1.38-2.14)	1.97 (1.79-2.44)	1.77 (1.36-2.04)	0.149	0.404
<65 (n=59)	1.77 (1.29-2.63)	1.92 (1.41-2.64)	1.65 (1.16-2.63)	0.391**	0.577
Sepsis diagnosis					
Present (n=53)	1.84 (1.26-2.38)	1.97 (1.41-2.44)	1.62 (1.05-2.01)	0.06	0.841
Absent (n=44)	1.88 (1.41-2.70)	1.92 (1.44-2.90)	1.82 (1.38-2.47)	0.845**	**
CV SOFA score					
≥3 (n=80)	1.90 (1.38-2.46)	1.95 (1.46-2.55)	1.80 (1.14-2.27)	0.237**	**
<3 (n=17)	1.59 (1.32-2.33)	2.17 (1.01-2.73)	1.52 (1.38-1.73)	0.671**	**

Shown are the median (IQR) of the mean delivered UF_{NET} rate according to the prespecified subgroups.

* Models adjusted for differences in age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, sepsis, and baseline cardiovascular SOFA score, excluding the relevant subgroup.

** Model did not converge. For unadjusted p-values, the Wilcoxon rank sum test p-value is shown instead.

eTable 8: Post-hoc Sensitivity Analysis

Characteristic	All	Liberal	Restrictive	P value	Adjusted P value*
First 7 days (n=97)					
Delivered UF_{NET} Mean (SD)	1.97 (0.85)	2.06 (0.82)	1.85 (0.88)	0.18	0.53
Delivered UF_{NET} Median (IQR)	1.89 (1.38-2.44)	1.97 (1.41-2.56)	1.71 (1.36-2.22)	-	-

* Models adjusted for differences in age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, sepsis, and baseline cardiovascular SOFA score.

eTable 9: Protocol Adherence

Protocol Adherence	All	Liberal	Restrictive	P value[a]	Adjusted P value[b]
Mean no. of hours UF_{NET} rate lower than the study protocol per day, mean (SD)	8.81 (5.82)	10.15 (5.72)	6.93 (5.49)	0.3	<0.001
Mean no. of episodes UF_{NET} rate lower than study protocol for 6 continuous hours per day, mean (SD)	1.11 (0.29)	1.16 (0.34)	1.01 (0.03)	0.08	0.8
Mean no. of hours UF_{NET} rate higher than the study protocol per day, mean (SD)	9.59 (4.48)	9.08 (5.29)	9.74 (4.29)	0.5^	***
Mean no. of episodes UF_{NET} rate higher than study protocol for 6 continuous hours per day, mean (SD)	1.07 (0.18)	1.06 (0.18)	1.07 (0.18)	0.6^	***
Mean no. of episodes UF_{NET} rate higher or lower than the study protocol for 6 continuous hours per day, mean (SD)	4.23 (6.10)	3.55 (4.27)	5.12 (7.85)	0.5^	***
No. of days UF_{NET} out of range for 6 continuous hours per patient, mean (SD)	3.63 (5.05)	2.98 (3.70)	4.48 (6.36)	0.3	0.7
At least 1 episode of UF_{NET} out of range for 6 continuous hours, no. (%)	81 (83.5%)	45 (81.8%)	36 (85.7%)	0.7	0.3
Proportion of hours UF_{NET} rate below range, mean (SD)	0.36 (0.33)	0.55 (0.30)	0.11 (0.16)	<0.001	-
Proportion of hours UF_{NET} rate within range, mean (SD)	0.42 (0.29)	0.41 (0.28)	0.44 (0.30)	0.006^	-
Proportion of hours UF_{NET} rate above range	0.22 (0.29)	0.04 (0.10)	0.44 (0.31)	<0.001	-

[a] Unadjusted P values calculated from a linear mixed model with a random effect for center and patient ID.

[b] Linear mixed models accounting for center, patient ID, and the following covariates: age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, sepsis, and baseline cardiovascular SOFA score.

^ Mixed model did not converge. P-value from unadjusted Wilcoxon test (continuous variables) or Fisher's exact test (binary variables).

*** Mixed model did not converge.

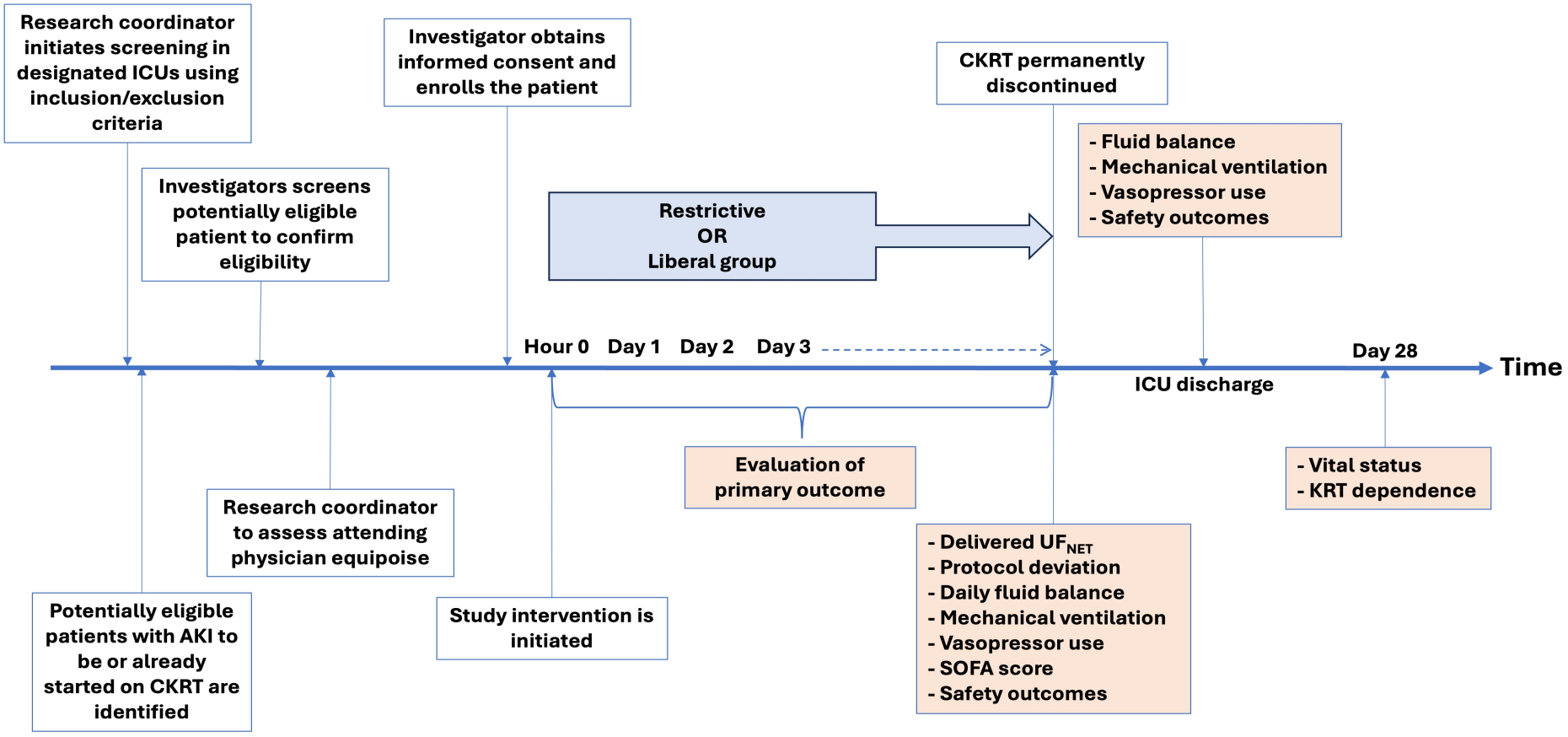
eTable 10: Safety Outcomes

Safety Outcomes	No. (%)			P value	Adjusted P value[a]
	All (N=97)	Liberal (N=55)	Restrictive (N=42)		
Intradialytic hypotension	76 (78.4)	44 (80.0)	32 (76.2)	0.6	0.7
No. of episodes per patient per day, mean (SD)	1.2 (0.5)	1.2 (0.6)	1.1 (0.4)		
Intradialytic hypertension	25 (25.8)	16 (29.1)	9 (21.4)	0.2	0.9
No. of episodes per patient per day, mean (SD)	1.0 (0.3)	1.0 (0.3)	1.0 (0.0)		
Cardiac arrhythmias	15 (15.5)	12 (21.8)	3 (7.1)	0.059	0.4
No. of episodes per patient per day, mean (SD)	0.9 (0.4)	0.9 (0.5)	0.8 (0.3)		
Use of rescue net ultrafiltration	36 (37.1)	8 (14.5)	28 (66.7)	<0.001	<0.001
No. of episodes per patient per day, mean (SD)	1.0 (0.4)	0.9 (0.2)	1.1 (0.5)		
Severe hypophosphatemia (<0.5 mg/dL)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Severe hypokalemia (<3.0 mg/dL)	1 (1.0)	0 (0.0)	1 (2.4)	0.9	1.0
Severe hypocalcemia (<1.90 mg/dL)	2 (2.1)	1 (1.8)	1 (2.4)	0.8	0.9
Hemofilter clotting or clogging	42 (43.3)	22 (40.0)	20 (47.6)	0.3	0.7
UF_{NET} discontinuation due to hemodynamic instability	47 (48.5)	25 (45.5)	22 (52.4)	0.5	0.8
Surgical wounds edema	1 (1.0)	1 (1.8)	0 (0.0)	1.0	**
New organ dysfunction	55 (56.7)	34 (61.8)	21 (50.0)	0.3	0.8
Worsening cardiac function	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Worsening of pulmonary edema	10 (10.3)	6 (10.9)	4 (9.5)	0.5	0.4
Worsening of ileus	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Bowel ischemia or anastomotic breakdown	2 (2.1)	1 (1.8)	1 (2.4)	0.8	0.9
New pressure ulcerations	0 (0.0)	0 (0.0)	0 (0.0)	-	-
New wound infections	1 (1.0)	1 (1.8)	0 (0.0)	1.0	**
New arterial thrombosis	1 (1.0)	0 (0.0)	1 (2.4)	0.9	**
New venous thrombosis	1 (1.0)	1 (1.8)	0 (0.0)	1.0	**
Severe anemia	43 (44.3)	27 (49.1)	16 (38.1)	0.3	0.2
Severe thrombocytopenia	21 (21.6)	15 (27.3)	6 (14.3)	0.1	0.5
New secondary infections	7 (7.2)	4 (7.3)	3 (7.1)	0.9	0.1

[a] Adjusted for differences in age, baseline eGFR, APACHE-III score, Elixhauser Comorbidity Index score, mechanical ventilation, admission source, sepsis, and baseline cardiovascular SOFA score.

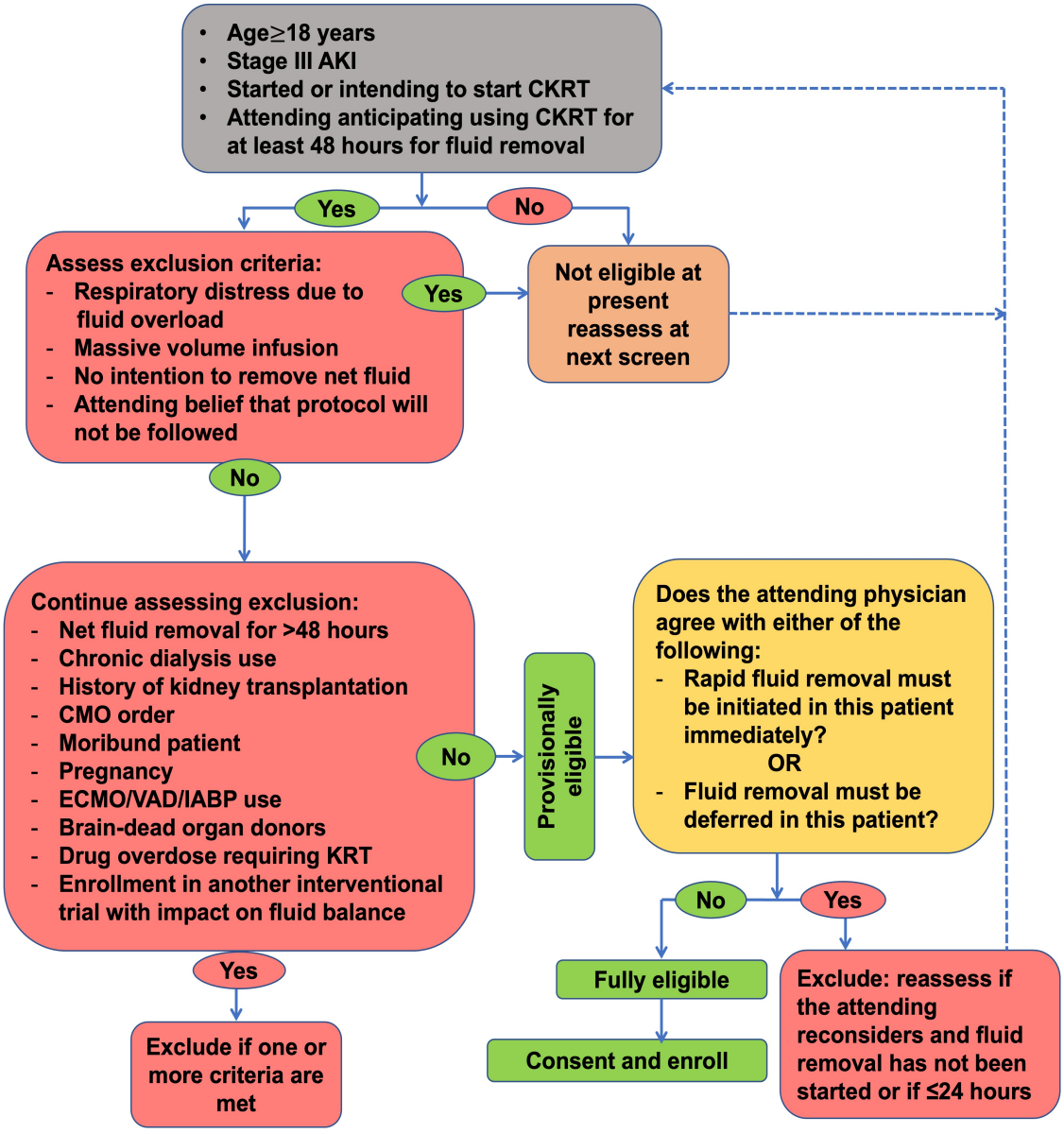
** Mixed model non-convergent.

eFigure 1: Study Procedures

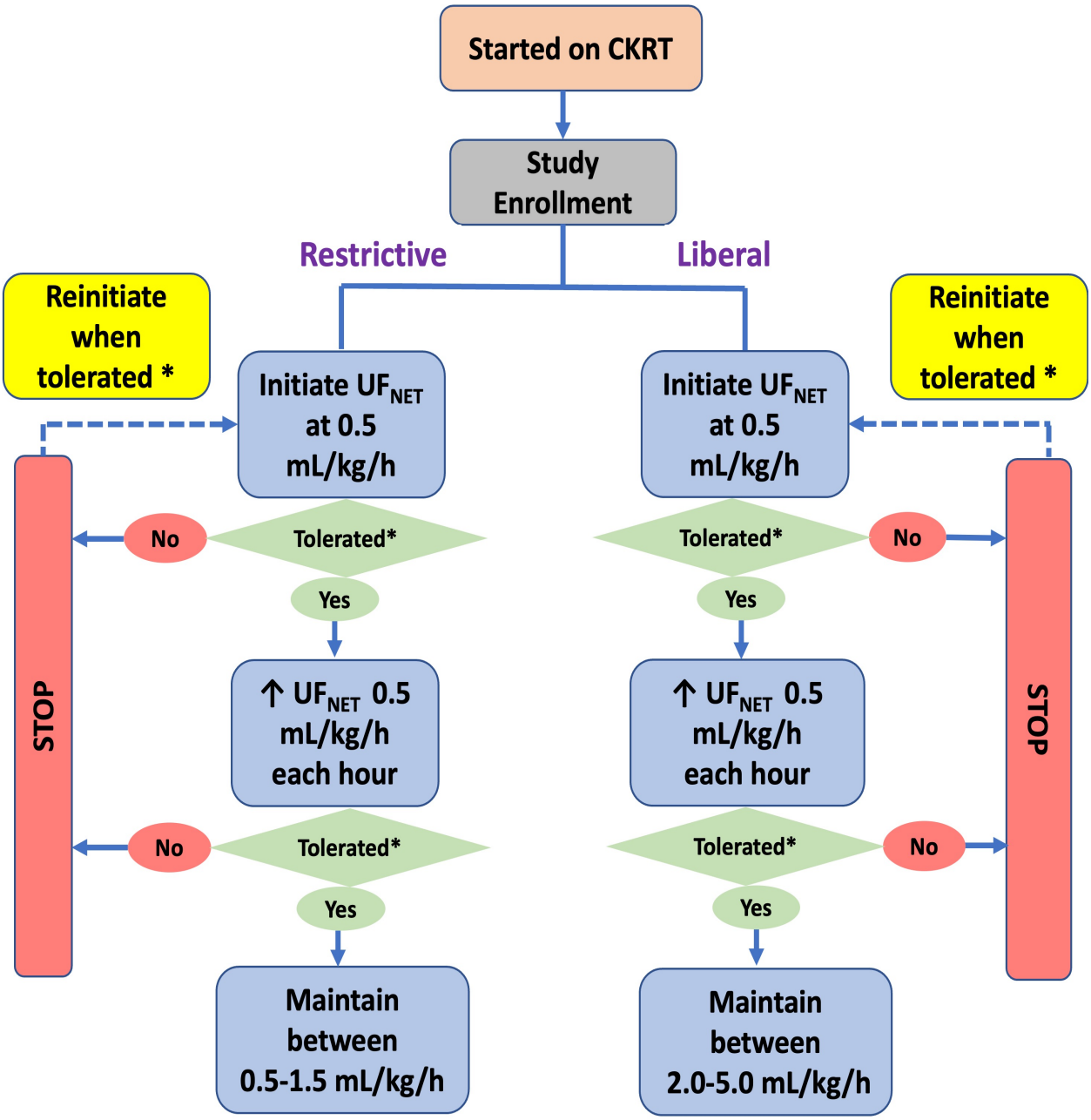


CKRT, continuous kidney replacement therapy; UF_{NET}, delivered net ultrafiltration; SOFA, sequential organ failure assessment; KRT, kidney replacement therapy; ICU, intensive care unit

eFigure 2: Assessment of Physician Equipoise

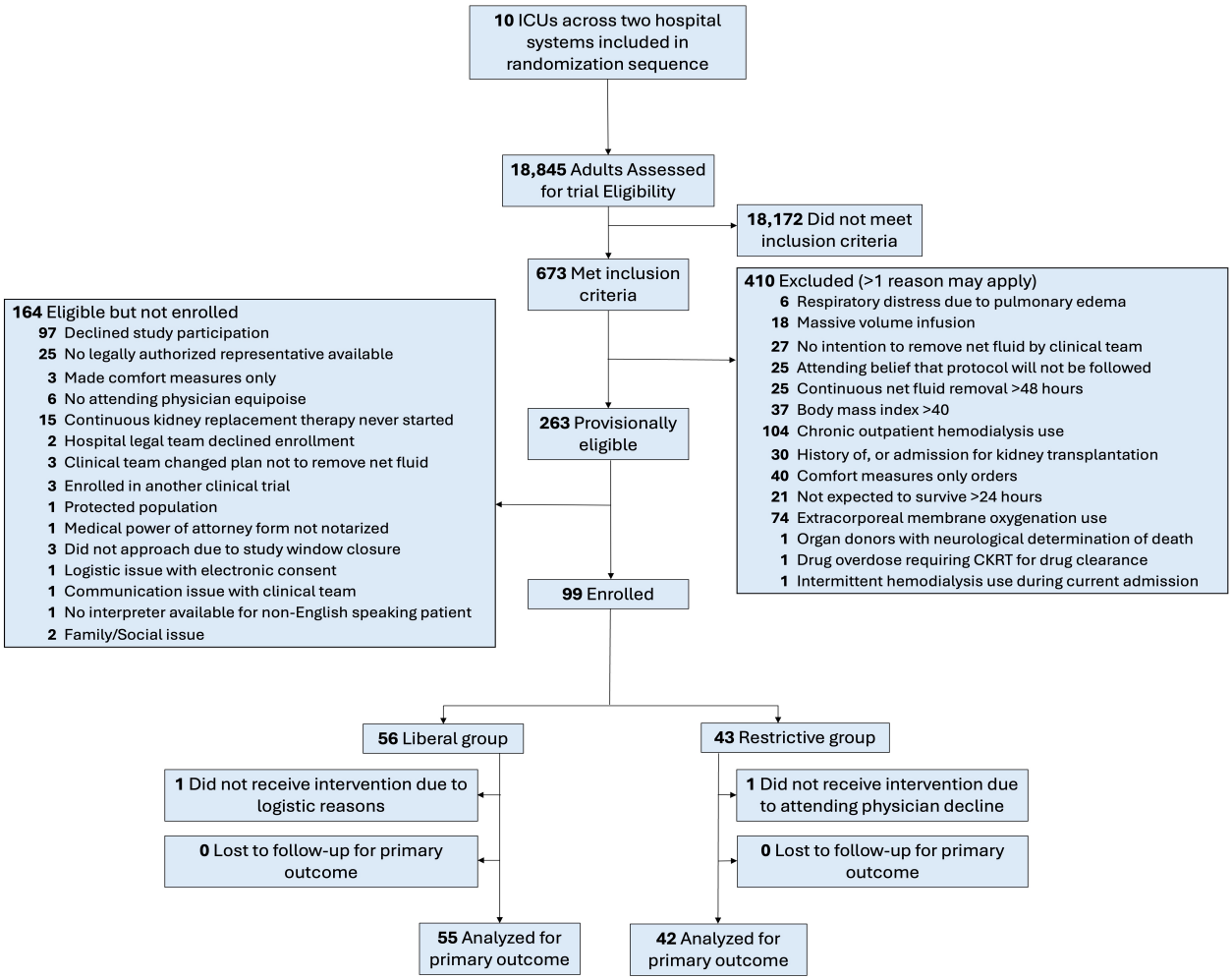


eFigure 3: Study Intervention



* Tolerance assessed by MAP ≥65 mmHg and systolic blood pressure ≥90mmHg

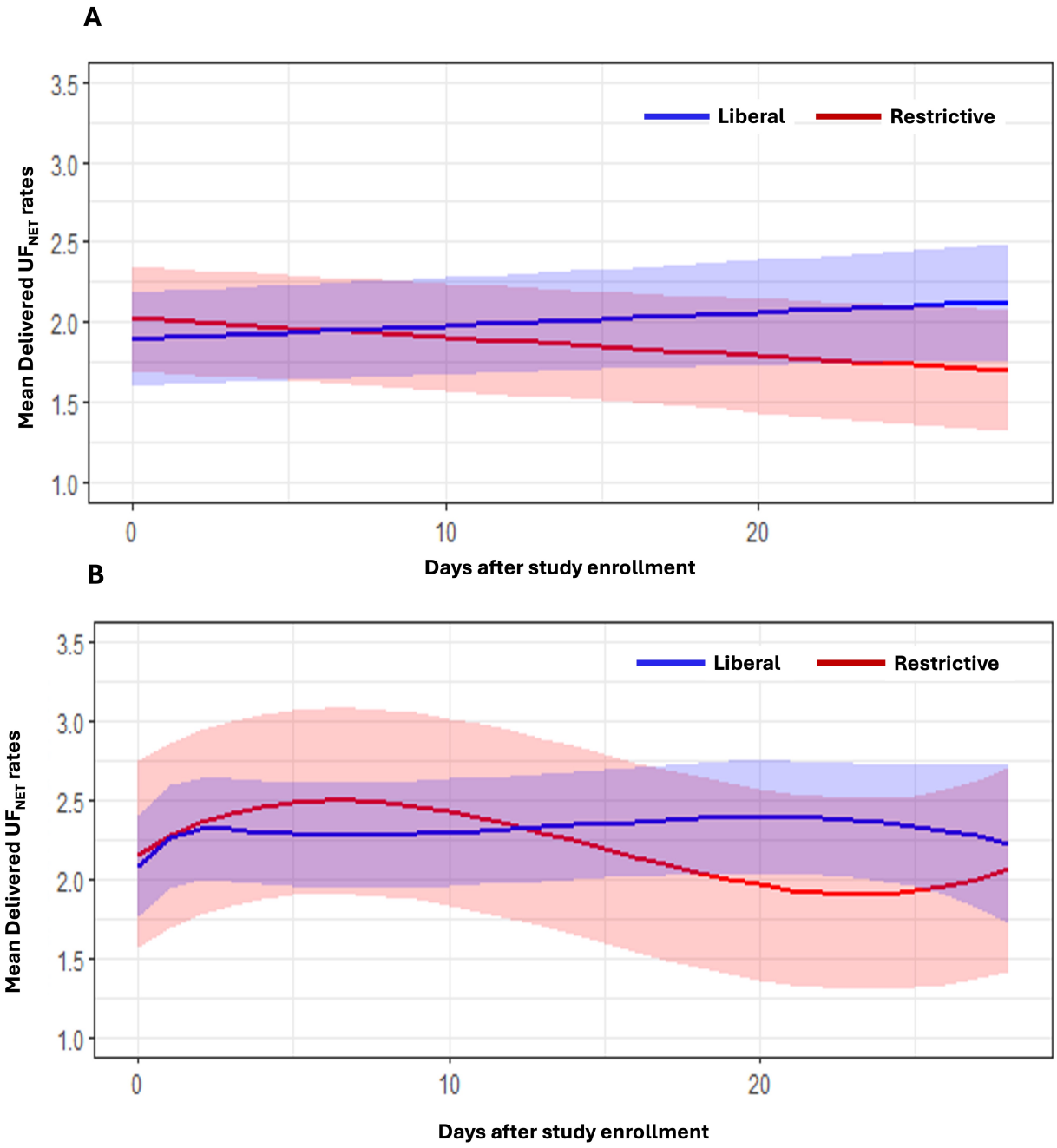
eFigure 4: Intensive Care Units and Individual Participants in the RELIEVE-AKI



	No. of Patients										
ICU	**Step 1**	**Step 2**	**Step 3**	**Step 4**	**Step 5**	**Step 6**	**Step 7**	**Step 8**	**Step 9**	**Step 10**	**Total**
1	2	1	0	1	1	1	2	0	0	1	**9**
2	1	0	1	1	0	0	0	0	0	1	**4**
3	0	3	1	3	1	1	2	5	3	0	**19**
4	1	1	4	1	1	3	3	0	0	0	**14**
5	2	1	0	2	1	1	0	0	2	1	**10**
6	0	0	2	2	0	2	0	2	1	0	**9**
7	3	1	3	1	3	1	1	1	2	0	**16**
8	0	0	1	0	0	0	1	1	0	0	**3**
9	2	0	1	3	2	1	1	0	1	1	**12**
10	0	1	2	0	0	0	0	0	0	0	**3**
Total	**11**	**8**	**15**	**14**	**9**	**10**	**10**	**9**	**9**	**4**	**99**

Step 1 lasted 6 months, beginning on July 5th, 2022. Steps 2 to 10 lasted 2 months, with Step 10 ending on June 17th, 2024, a total of 23 months and 12 days. The two-month duration excluded weekends, federal holidays, and university holidays. Blue shading indicates a transition from the liberal group to the restrictive group.

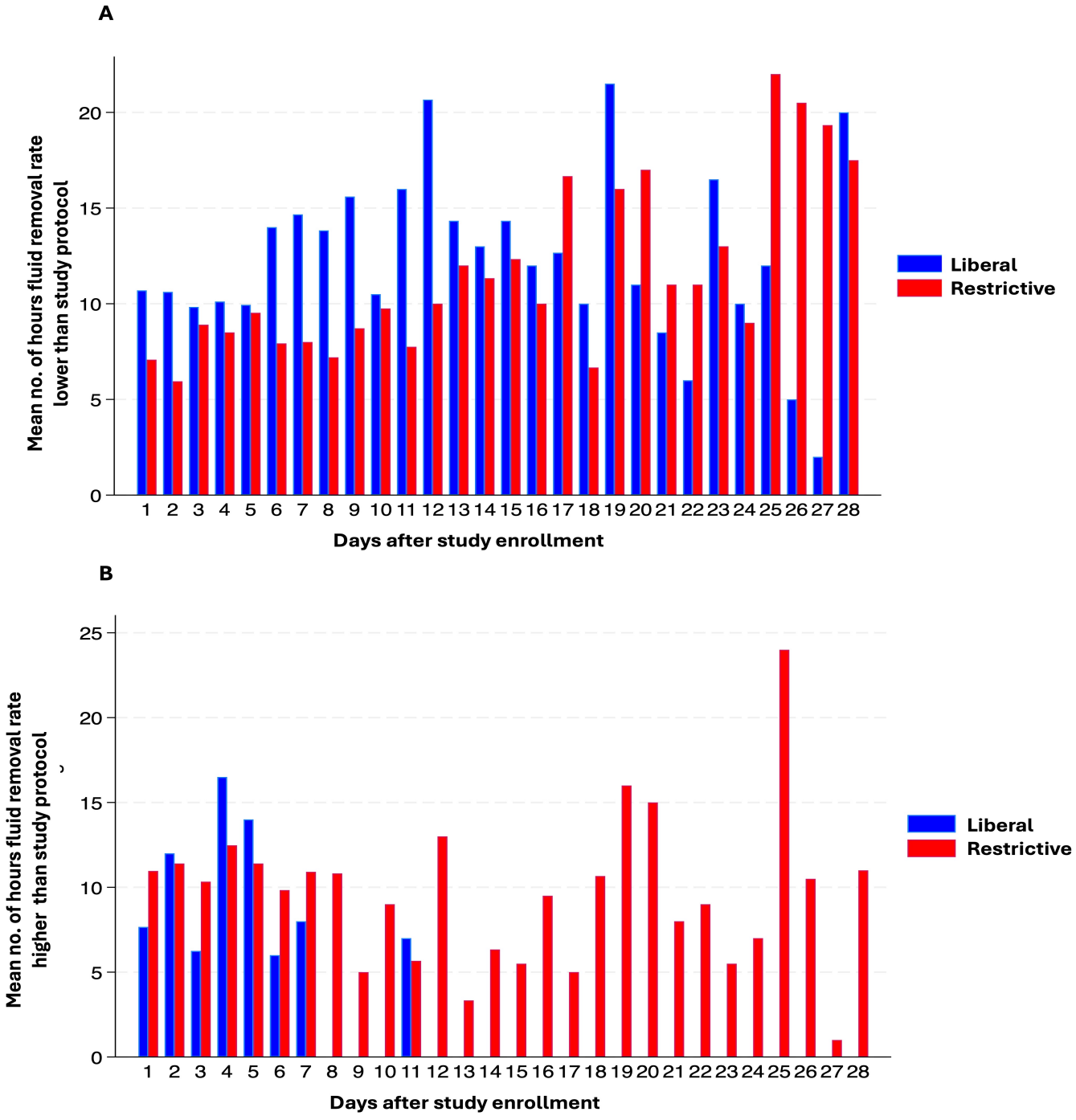
eFigure 5: Longitudinal Modeling of UF_{NET} rate Trajectories



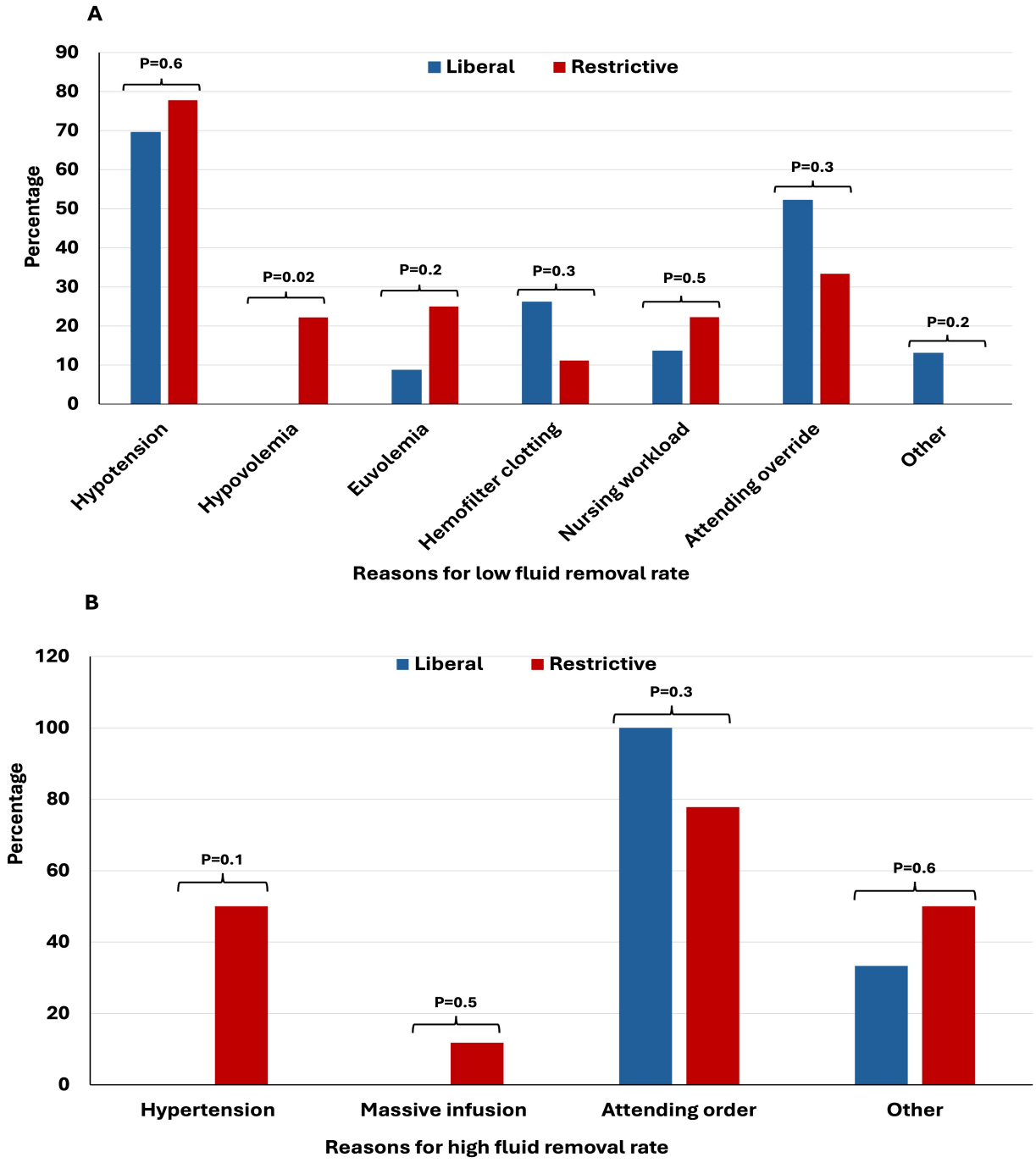
To evaluate the longitudinal trends of delivered UF_{NET} rates between the liberal and restrictive groups, we employed adjusted linear mixed models (A). Initial linear modeling indicated no significant difference between groups at Day 0 (P=0.6). However, the restrictive group demonstrated a significant decline in mean UF_{NET} rates over the study period (P=0.003), whereas the liberal group exhibited a significantly different trajectory, characterized by a higher and increasing rate of change over time (P<0.001).

To further account for non-linear temporal patterns, a cubic spline model was utilized (B). A likelihood ratio test confirmed a significant interaction between group assignment and the spline over time ($P<0.001$), providing strong statistical evidence that UF_{NET} trajectories diverged between the two groups. Notably, despite these differing longitudinal patterns, 95% confidence intervals for the two groups overlapped throughout the observation period, suggesting that mean values remained within similar ranges despite diverging trends.

eFigure 6: Mean No. of Hours Fluid Removal Rate Lower or Higher than Study Protocol

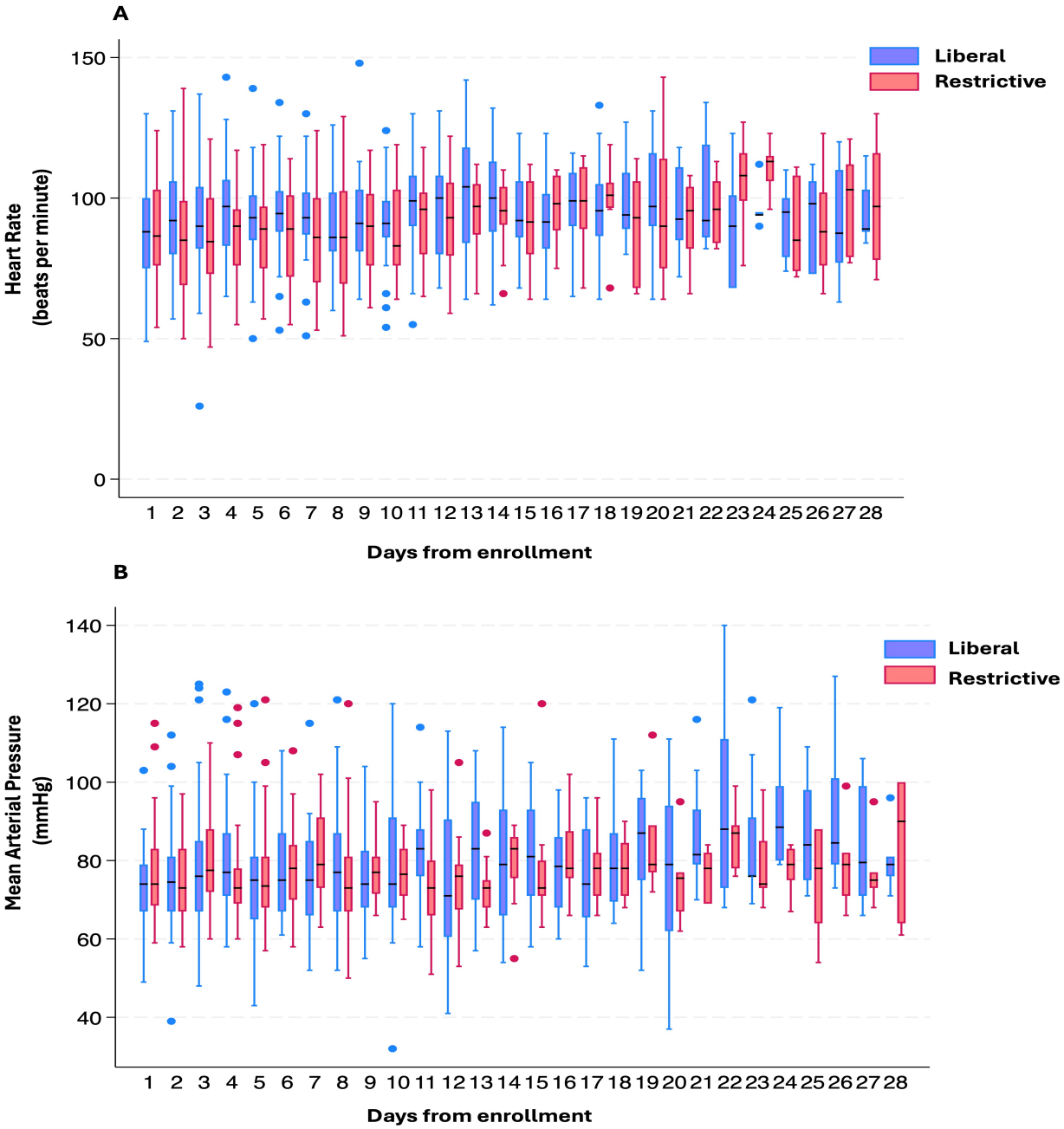


eFigure 7: Clinical Reasons for Deviation from Study Protocol



A. Clinical reasons for lower rate of fluid removal than the target range for 6 continuous hours by liberal vs. restrictive group.
B. Clinical reasons for higher rate of fluid removal than the target range for 6 continuous hours by liberal vs. restrictive group.

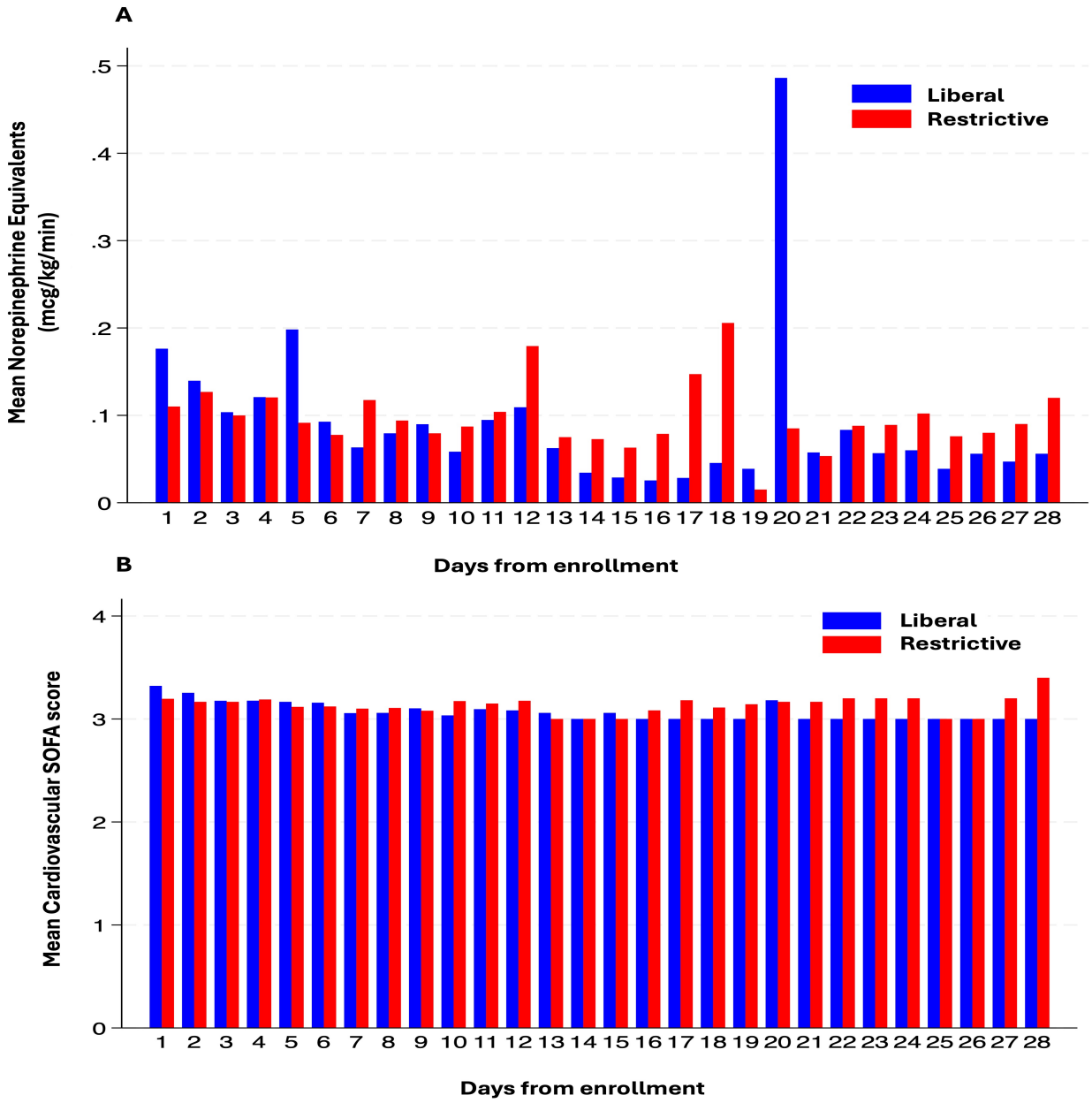
eFigure 8: Hemodynamic Parameters



A. There was a small difference in heart rate. The liberal group had a higher heart rate than restrictive group (93.5 [17.23] vs. 91.2 [40.7] beats per minute, P=0.2; adjusted P=0.04) accounting for patient ID and ICU via random effects.

B. There was no difference in the mean arterial pressure between the liberal vs. restrictive group (78.52[15.6] vs. 78.5[34.6]; P=0.6; adjusted model failed to converge.

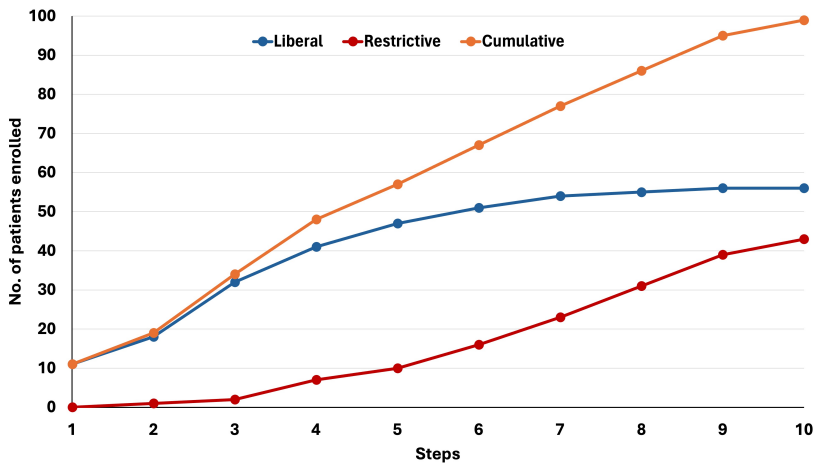
eFigure 9: Vasopressor Dose and Cardiovascular SOFA Score

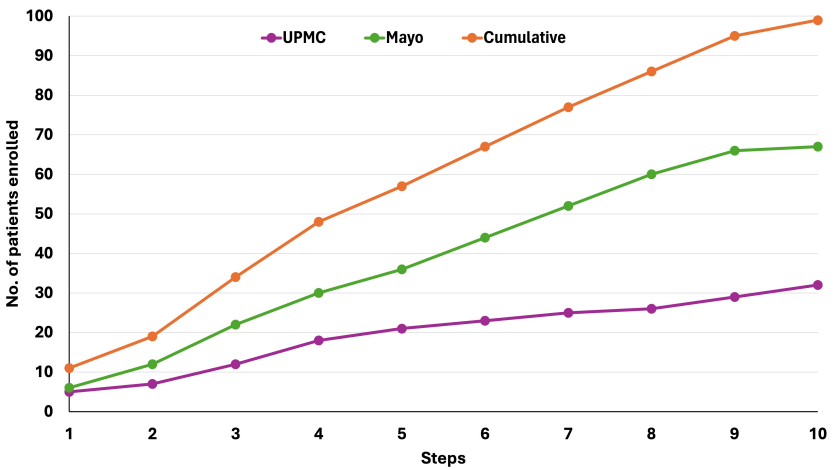


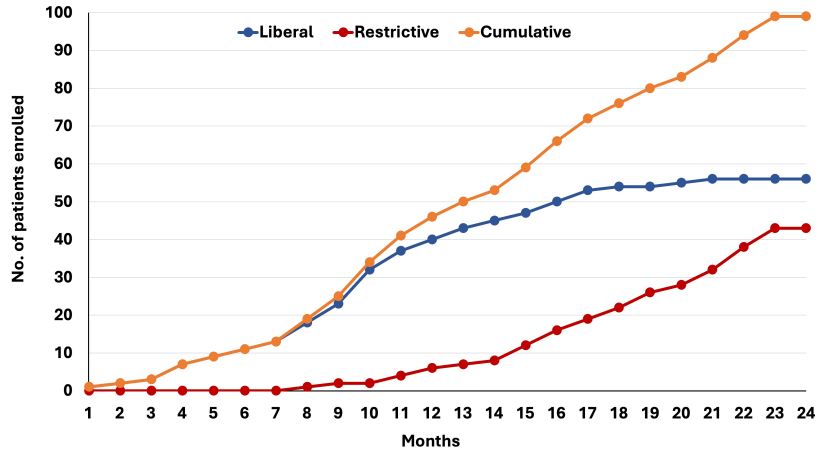
A. Vasopressor doses were standardized in terms of norepinephrine equivalents (NE) (mcg/kg/min) except vasopressin (units/min) using the following equation.[13] NE = Norepinephrine + epinephrine + (phenylephrine/10) + (dopamine/100) + (Vasopressin*2.5) + (Angiotensin-II/10). There was no difference in the mean (SD) vasopressor dose between liberal vs. restrictive group (0.10 [0.23] vs. 0.10 [0.13] norepinephrine equivalents; P=0.6; adjusted P=0.3).

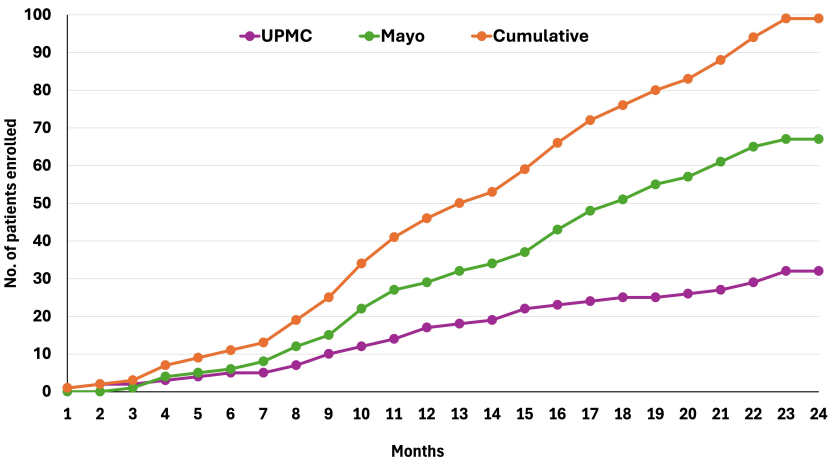
B. There was no difference in mean (SD) cardiovascular SOFA score between liberal vs. restrictive group (3.1 [0.32] vs. 3.1 [0.34]), P=0.6; adjusted P=0.4)

eFigure 10: Recruitment Rate by Step and Month of Enrolment

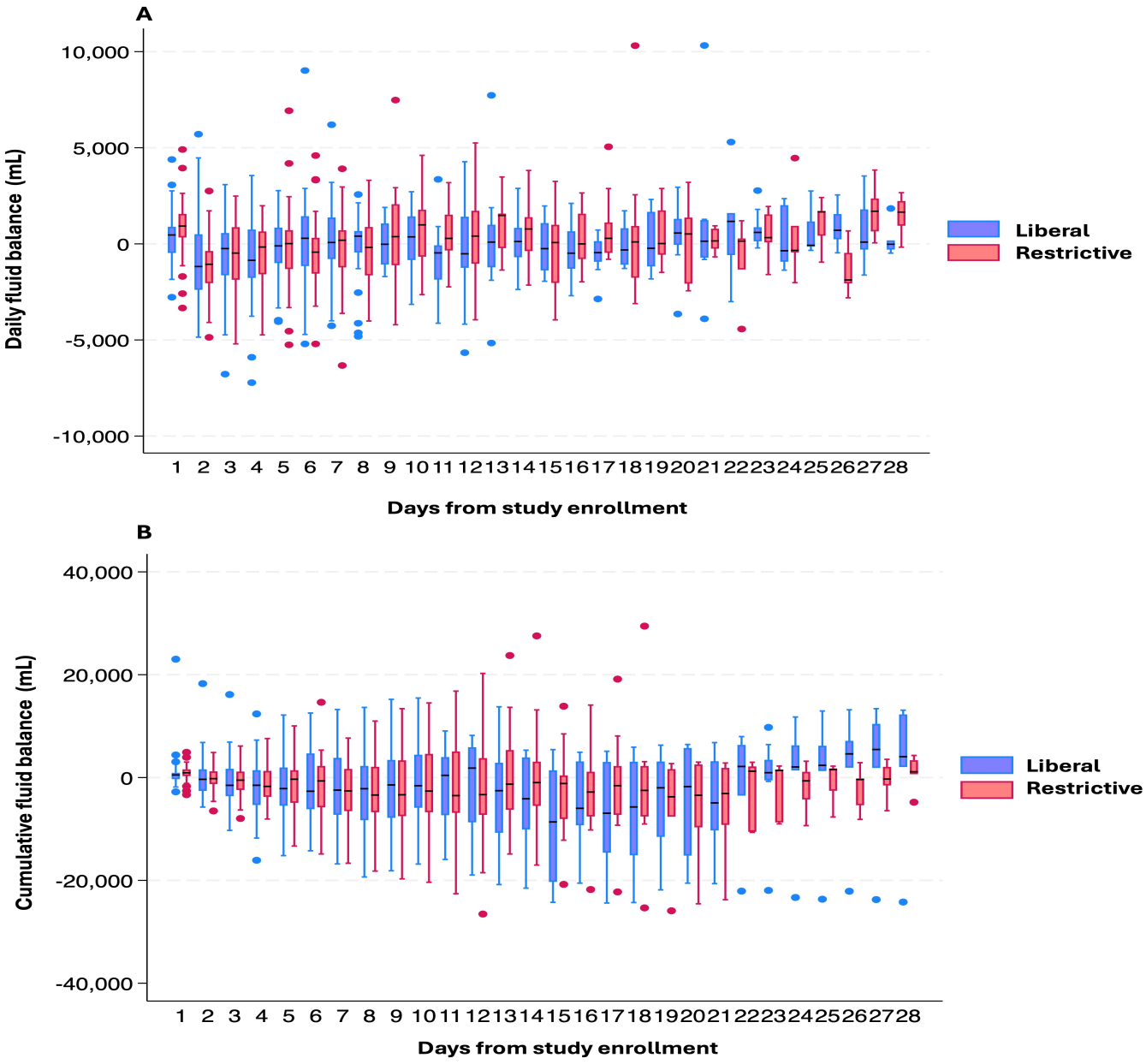




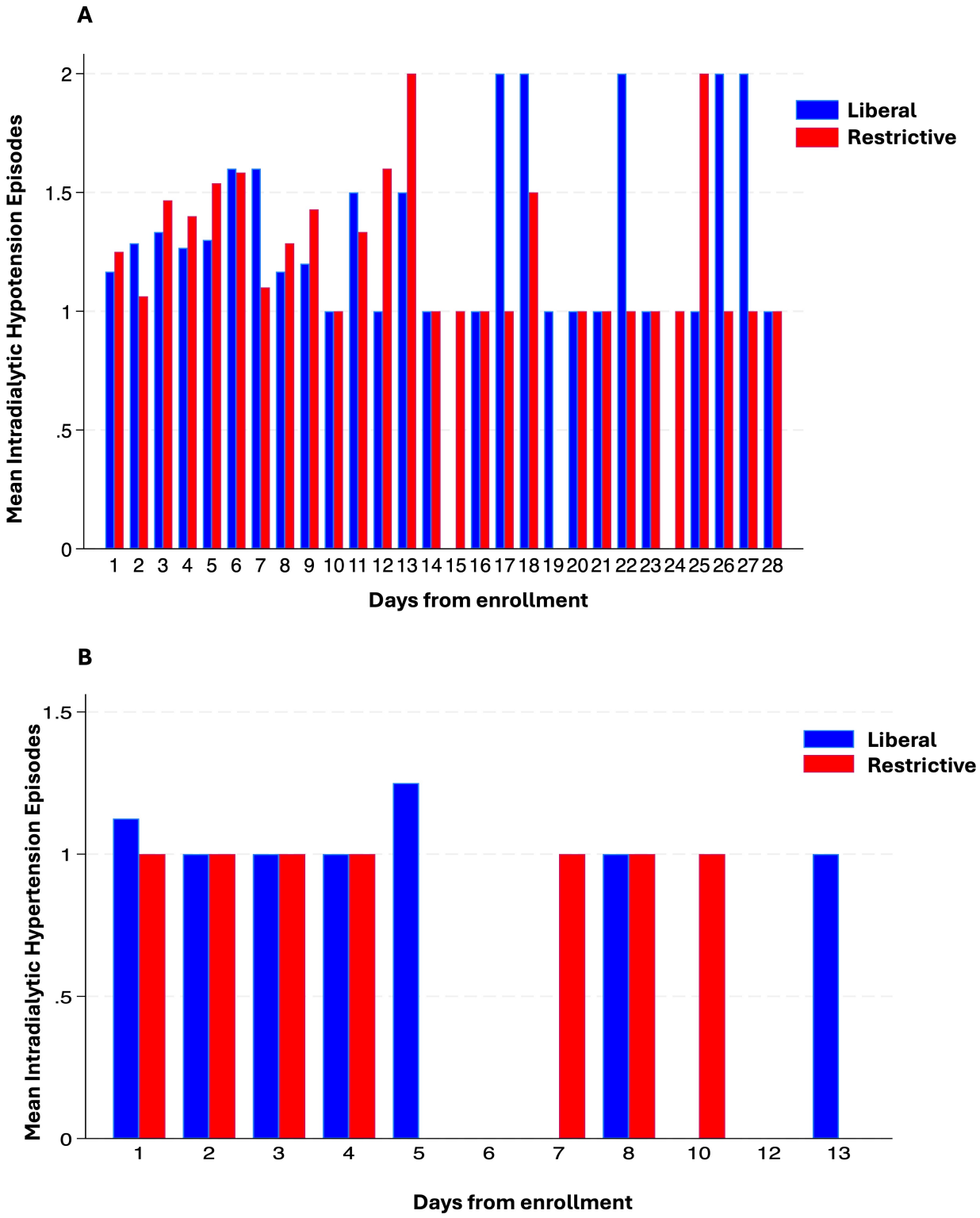




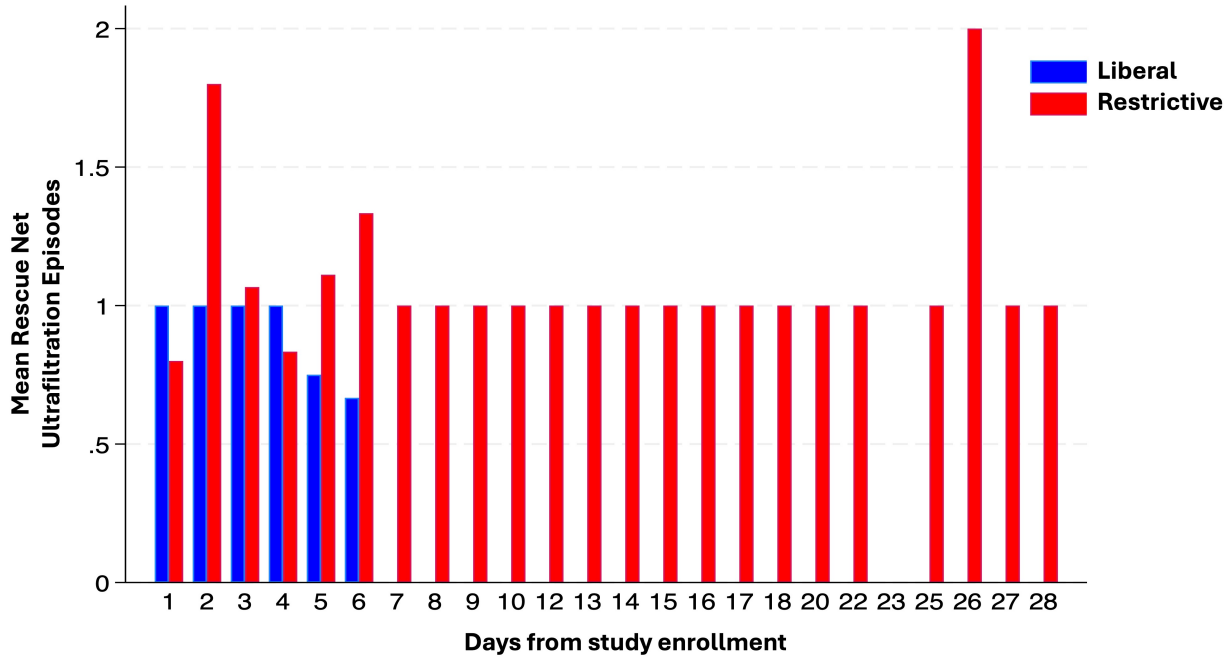
eFigure 11: Daily and Cumulative Fluid Balance



eFigure 12: Intradialytic Hypotension and Hypertension Episodes



eFigure 13: Rescue Net Ultrafiltration Episodes



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