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Volume removal **I**ntolerance during **N**et ultrafiltration in Acute **K**idney injury patients

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1.- INTRODUCTION

Fluid balance management in critically ill patients with acute kidney injury (AKI) represents a fundamental therapeutic challenge. Fluid overload is associated with worse outcomes, including increased mortality, prolonged mechanical ventilation, and reduced recovery of kidney function [1]. In this context, net ultrafiltration (UF^{NET}) through continuous renal replacement therapy (CRRT) is a key “de-resuscitation” strategy. However, hemodynamic tolerance to ultrafiltration is highly variable, and its prediction remains poorly defined [2,3].

Traditionally, the debate surrounding net ultrafiltration has focused on the intensity or rate of fluid removal, particularly on UF^{NET} thresholds adjusted by body weight. Early observational studies suggested that higher UF^{NET} rates (>1.7 mL/kg/h) might be associated with greater hemodynamic instability and worse outcomes, leading to a cautious approach to fluid removal in critically ill patients [4]. However, more recent evidence has challenged the notion that ultrafiltration rate per se is the main determinant of harm. On the contrary, contemporary data indicate that failure to achieve prescribed fluid removal targets—whether due to intradialytic hypotension or repeated interruptions of therapy—is consistently associated with persistent positive fluid balance, organ congestion, and increased mortality. These findings suggest that the risk does not necessarily lie in “removing fluid too quickly,” but rather in failing to achieve effective de-resuscitation because the patient cannot tolerate ultrafiltration, thereby perpetuating fluid overload and its pathophysiological consequences [5–7].

The concept of “ultrafiltration intolerance” currently lacks a standardized or widely accepted definition. By analogy with the concept of fluid tolerance, ultrafiltration tolerance can be defined as the ability of a patient to undergo ultrafiltration without developing hemodynamic instability, tissue hypoperfusion, or new-onset organ dysfunction. Within this framework, ultrafiltration intolerance reflects either a limited physiological reserve

and/or an ultrafiltration prescription that is not adequately tailored to the patient's hemodynamic and perfusion status.

In clinical practice, and in the absence of uniform criteria for ultrafiltration intolerance, this concept is often interpreted in its final stage as hemodynamic instability related to renal replacement therapy (HIRRT), a frequent complication that may occur in up to 60–70% of patients undergoing dialysis therapies in critical care settings [8]. HIRRT has been identified as an independent predictor of mortality in critically ill patients and is typically defined based on macrohemodynamic parameters, such as intradialytic hypotension or the need for therapeutic interventions (fluid administration, vasopressors, or interruption of therapy). Its incidence varies depending on the modality of extracorporeal support, with a frequency of approximately 40–60% in prolonged low-efficiency dialysis sessions and 19–43% in CRRT treatments [9–15].

Beyond its high frequency, HIRRT represents the main barrier to effective fluid removal and is consistently associated with persistent positive fluid balance and worse clinical outcomes [16,17]. However, strategies commonly used to address intradialytic hypotension are often reactive rather than preventive, focusing on late correction of overt instability [18]. This approach is limited, as hemodynamic monitoring during RRT is largely based on blood pressure, a relatively insensitive marker of circulatory compromise. Indeed, cardiac output is not routinely monitored, and there is robust evidence that significant decreases in cardiac output may occur early during ultrafiltration, even in the absence of hypotension, with blood pressure being maintained through compensatory increases in systemic vascular resistance [19]. In this context, intradialytic hypotension represents a late event, occurring only when vasoconstrictive reserve is exhausted, at which point organ perfusion may already be compromised.

These limitations highlight the need to move toward individualized ultrafiltration strategies, aimed not only at maintaining macrohemodynamic stability but also at preserving cardiac output and tissue perfusion, with the goal of preventing ultrafiltration intolerance, reducing the risk of organ injury, and potentially improving survival.

Several approaches have been proposed to assess ultrafiltration tolerance in an individualized manner, including ultrasound-based techniques (VEXUS protocol, inferior vena cava assessment, and echocardiography), aimed at estimating venous congestion, preload, and cardiac function; dynamic functional tests, such as passive leg raising (PLR), which allow identification of preload dependence and have demonstrated the ability to predict hemodynamic intolerance to fluid removal before the initiation of ultrafiltration; and circulating biomarkers, such as albumin, calcium, lactate, and B-type natriuretic peptide (BNP), the latter being used as an indirect marker of volume status and congestion [20–31]. Additionally, dynamic hemodynamic indices have been explored, including stroke volume variation (SVV), pulse pressure variation (PPV), and dynamic arterial elastance, as well as peripheral perfusion parameters [23,31–36]. In this context, both the peripheral perfusion index (PPI) and clinical markers of skin perfusion—particularly capillary refill time and the mottling score—have demonstrated utility in detecting early circulatory deterioration during ultrafiltration, identifying different hemodynamic profiles during fluid removal, and correlating with mortality.

These parameters are particularly relevant, as there is evidence that reductions in cardiac output and intravascular blood volume may precede overt hypotension, with blood pressure being maintained through compensatory mechanisms, thereby limiting the sensitivity of monitoring strategies based solely on blood pressure [37,38]. Taken together, these approaches encompass different domains of circulatory reserve and the interaction between cardiac output, vascular tone, tissue perfusion, and venous congestion during fluid removal [2,3].

In this context, there remains an unmet need to more precisely define ultrafiltration intolerance and to identify early markers that allow its prediction before the onset of overt hypotension. An integrated evaluation of multiple hemodynamic and perfusion domains—including macrohemodynamic parameters, dynamic indices, peripheral perfusion markers, and clinical variables—may provide a more sensitive and pathophysiologically coherent approach to characterizing the individual response to fluid removal.

Therefore, the present prospective and analytical study aims to evaluate the hemodynamic and perfusion changes before and during the early phases of net ultrafiltration in patients undergoing continuous renal replacement therapy, using a multiparametric monitoring strategy. Specifically, the study seeks to determine the incidence of ultrafiltration intolerance beyond isolated hypotension, analyze its association with different circulatory parameters, identify early predictors of instability, and characterize the hemodynamic profile of patients who develop intolerance, with the goal of advancing toward more individualized and physiologically guided ultrafiltration strategies.

2.- METHODS

2.1 Study Design

This is a prospective, observational, analytical case–control study conducted in critically ill adult patients undergoing CRRT, aimed at evaluating hemodynamic tolerance to net ultrafiltration using a multiparametric monitoring strategy.

Cases will correspond to patients who develop ultrafiltration intolerance during the observation window defined in the protocol. Controls will correspond to patients undergoing net ultrafiltration who do not develop intolerance during this period.
The objective of the study is to identify clinical, hemodynamic, ultrasound-based, perfusion-related, and biochemical factors associated with the development of ultrafiltration intolerance.

2.2 Study Population

2.2.1 Inclusion Criteria

- Adult patients (>18 years)
- Admission to the Intensive Care Unit
- Diagnosis of acute kidney injury according to KDIGO criteria
- Indication for CRRT with a prescription for net ultrafiltration
- Sufficient clinical stability to initiate ultrafiltration according to the treating team's judgment

2.2.2 Exclusion Criteria

- Patients on chronic renal replacement therapy
- Pregnancy
- Limitation of therapeutic effort or goals-of-care decisions at admission or during the observation period
- Inability to perform hemodynamic or perfusion assessment
- Patients on ECMO
- Refusal to participate in the study

2.3 Continuous Renal Replacement Therapy and Ultrafiltration

CRRT will be performed according to current institutional protocols, including modality (CVVH, CVVHD, or CVVHDF), anticoagulation, and dialysis prescription, all at the discretion of the treating team.

Net ultrafiltration will be prescribed by the treating physician according to the patient's clinical condition. The study does not interfere with therapeutic prescriptions nor modify routine clinical decision-making.

Net ultrafiltration (UFNET) is defined as the volume of fluid removed by the CRRT machine through ultrafiltration, calculated as the difference between total effluent and the fluids administered by the machine itself (dialysate and/or replacement solutions) [39].
Net ultrafiltration does NOT include:

- External fluid inputs (nutrition, medications, boluses, blood products)
- Residual urine output
- Drains, gastrointestinal losses, or other non-CRRT-related fluid losses

2.4 Hemodynamic and Perfusion Assessment (Multiparametric Monitoring)

Patients will be evaluated before the initiation of ultrafiltration and during the early hours of net ultrafiltration using a multiparametric monitoring strategy including:

a) Macrohemodynamic Variables

- Mean arterial pressure (MAP)
- Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), pulse pressure (PP), diastolic shock index (DSI)
- Heart rate
- Vasopressor dose and vasoactive-inotropic score (VIS), when applicable
- Sedative dose

b) Dynamic Hemodynamic Variables

- Stroke volume variation (SVV), when available
- Pulse pressure variation (PPV)
- Dynamic arterial elastance, when feasible

c) Ultrasound Assessment

- VEXUS protocol for venous congestion assessment
- Description of: hepatic vein, portal vein, and renal vein Doppler
- Splenic vein Doppler assessment
- Inferior vena cava evaluation
- Focused echocardiography to assess systolic function, velocity–time integral (VTI), cardiac index, and preload status based on VTI and cardiac output variations

d) Peripheral Perfusion Variables

- Capillary refill time

- Mottling score
- Peripheral perfusion index (PPI), when available

e) Biomarkers

- Serum lactate
- Albumin
- Calcium
- B-type natriuretic peptide (BNP), when available

f) Dynamic Functional Tests (performed before ultrafiltration initiation)

- Passive leg raising (PLR), when feasible
- Postural maneuver (e.g., sitting), when feasible

2.5 Definition of Ultrafiltration Intolerance

Ultrafiltration intolerance will be defined as the occurrence of one or more of the following criteria during the observation period:

- Hypotension associated with ultrafiltration, defined as systolic blood pressure <90 mmHg, or a decrease ≥10 mmHg from baseline if baseline was already <90 mmHg (see appendix)
- Need to increase vasopressor dose
- Worsening of peripheral perfusion parameters (capillary refill time >3 seconds, new onset or increase in mottling score, decrease in PPI)
- Evidence of tissue hypoperfusion: increase in lactate ≥0.5 mmol/L from T0 and absolute lactate >2 mmol/L, without alternative explanation [40]
- Need to reduce, stop, or interrupt ultrafiltration due to hemodynamic instability
- Exclusion of alternative causes of hypotension/hypoperfusion unrelated to therapy (e.g., bleeding, deep sedation). Attribution of alternative causes will be determined by the treating investigator and prospectively recorded in the case report form (CRF)

2.6 Study Outcomes

Primary Outcome

To determine the clinical, hemodynamic, ultrasound-based, perfusion-related, and biochemical factors associated with the development of ultrafiltration intolerance in critically ill patients with acute kidney injury undergoing CRRT with prescribed UF^{NET}, by comparing patients who develop intolerance (cases) versus those who do not (controls), according to the operational definition established in Section 2.5.

Observation Window

From T0 (initiation of UF^{NET}) to T6 hours, with measurements every 2 hours during the first 6 hours.

After 6 hours, measurements will be performed every 6 hours up to 24 hours or until interruption of UF^{NET}/CRRT, whichever occurs first.

During the observation window, the occurrence of any ultrafiltration intolerance criterion will trigger an immediate off-schedule recording using the abbreviated assessment set, without waiting for the next scheduled time point, even if this occurs outside predefined time intervals.

Note: Early events will be defined as those occurring within the first 6 hours, with particular emphasis on identifying early signs of ultrafiltration intolerance.

Secondary Outcomes

- To describe the incidence of ultrafiltration intolerance during the observation window
- To compare macrohemodynamic, ultrasound, peripheral perfusion, and biochemical parameters between patients with and without ultrafiltration intolerance
- To evaluate the association between peripheral perfusion parameters and hemodynamic variables with the presence of ultrafiltration intolerance

- To characterize pathophysiological profiles of ultrafiltration intolerance according to predominant features (hemodynamic compromise, peripheral perfusion deterioration, increased vasoactive support, or metabolic alterations)
- To explore the relationship between UF^{NET} rate and the development of ultrafiltration intolerance
- To assess agreement between intolerance defined by hypotension versus intolerance defined by hypoperfusion criteria
- To describe clinical outcomes, including cumulative fluid balance at 24 hours, achieved UF^{NET}, therapy interruptions, renal recovery, ventilator-free days, and ICU/hospital mortality
- To characterize timing of onset (early vs late; e.g., <6 hours vs ≥6 hours)
- To assess severity of intolerance (clinical grading)

Severity classification (3 levels):

- **Mild:** signs of hypoperfusion/peripheral perfusion impairment without need for major therapeutic intervention
- **Moderate:** need for intervention (UF^{NET} reduction, fluid administration, or vasopressor adjustment) without complete interruption
- **Severe:** suspension/interruption of UF^{NET} or therapy due to instability or hypoperfusion

2.7 Statistical Analysis

Statistical analysis will be performed using IBM SPSS Statistics v25 and Python. A descriptive and analytical approach will be used to compare patients with ultrafiltration intolerance (cases) versus those without intolerance (controls), and to identify factors associated with this outcome.

In Python, standard libraries will be used, including:

- **pandas** and **numpy** for data handling
- **scipy** for non-parametric statistics
- **statsmodels** for statistical modeling
- **matplotlib** for data visualization

2.7.1 Data Preparation and Quality Control

- Data consistency, physiological ranges, and clinical plausibility will be verified for all variables

Missing data handling:

- Variables with >25% missing data will be excluded from inferential analysis
- Variables with ≤25% missing data will be analyzed using available-case analysis

2.7.2 Descriptive Statistics

- Continuous variables will be expressed as median and interquartile range (IQR)
- Categorical variables will be expressed as frequency and percentage

2.7.3 Normality Assessment

Normality of continuous variables will be assessed using:

- Shapiro–Wilk test

Given the expected non-normal distribution of hemodynamic variables in critically ill patients, inferential analysis will be conducted using non-parametric statistics.

2.7.4 Group Comparisons

Patients will be classified according to:

- Development of ultrafiltration intolerance (yes vs no)
- Timing of intolerance (early ≤6 hours vs late >6 hours)

Comparisons will be performed as follows:

- Continuous variables: Mann–Whitney U test
- Categorical variables: Chi-square test or Fisher’s exact test, as appropriate

2.7.5 Identification of Predictors

Associations between baseline demographic variables, relevant comorbidities, and baseline clinical, ultrasound, hemodynamic, perfusion, and biochemical parameters—as well as their early changes during the first hours of ultrafiltration (up to T6)—with the development of ultrafiltration intolerance will be evaluated.

A bivariate analysis will first be conducted to explore associations between these variables and ultrafiltration intolerance.

Subsequently, clinically relevant variables or those associated in the bivariate analysis will be included in a multivariable logistic regression model to identify independent predictors of early ultrafiltration intolerance.

Covariate selection will be based on clinical relevance and number of events, in order to avoid model overfitting.

Results will be expressed as adjusted odds ratios (OR) with 95% confidence intervals, considering a p-value <0.05 as statistically significant.

2.7.9 Significance Level

A two-sided p-value <0.05 will be considered statistically significant.

2.8 Sample Size

Given that the primary objective of the study is to identify factors associated with ultrafiltration intolerance, sample size was calculated using an analytical case–control approach, considering as the main predefined exposure the presence of baseline preload dependence, defined by a positive passive leg raising test prior to UF^{NET} initiation.

Following standard approaches for analytical studies, the proportion of exposure in controls (P2) was assumed to be 25%, with a minimum clinically relevant odds ratio of 3.0, a two-sided significance level of 5%, statistical power of 80%, and a 1:1 case–control ratio. Under these assumptions, the expected proportion of exposure in cases (P1) was 50%, resulting in an estimated sample size of 58 patients per group (116 patients total). Considering potential losses, incomplete data, or inability to definitively adjudicate outcomes, an approximate 10% over-recruitment is planned, with a target sample size of 128 patients.

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \left[P_1(1-P_1) + P_2(1-P_2)\right]}{(P_1 - P_2)^2}$$

Where:

- *n* = number of patients per group
- *P1* = proportion of exposure in cases
- *P2* = proportion of exposure in controls
- *Z*α/2 = value corresponding to the significance level (1.96 if α = 0.05)
- *Z*β = value corresponding to statistical power (0.84 if power = 80%)

3. Ethical Considerations

The present study will be submitted for evaluation and approval by the Scientific Ethics Committee of the Talcahuano Health Service and will be conducted in accordance with the ethical principles established in the Declaration of Helsinki, the CIOMS Guidelines, and current national regulations, particularly the Chilean Ministry of Health Technical Standard No. 0151/2013 for research involving human subjects.

This is an observational, analytical, and non-interventional study, based on the collection of clinical, hemodynamic, ultrasound, and functional data obtained as part of the routine management of critically ill patients with acute kidney injury undergoing continuous renal replacement therapy. The study does not involve additional procedures, modifications to therapeutic management, or interventions beyond standard clinical practice in the Intensive Care Unit.

3.1 Data Management and Anonymization

Data will be collected from the institutional medical records and subsequently anonymized prior to inclusion in the research database. No direct or indirect identifiable information will be stored in the final dataset.

Access to the data will be restricted to the authorized research team, who will ensure data protection through appropriate security measures, including password protection and storage on institutional devices, in compliance with current regulations on confidentiality and protection of sensitive data.

3.2 Social Value of the Research

This study has high social and clinical value, as it aims to identify clinical, hemodynamic, and perfusion predictors of ultrafiltration intolerance in critically ill patients. The results may contribute to a more individualized and physiologically guided prescription of ultrafiltration, with the potential to reduce adverse events related to hemodynamic instability and improve the safety of CRRT.

The evidence generated may help optimize the management of critically ill patients at a local level and, potentially, at national and international levels, particularly in high-complexity and resource-limited settings. This collective benefit provides ethical justification for conducting the study, in accordance with the principles of proportionality, beneficence, and non-maleficence.

4. Funding and Budget

The present study does not have external funding. All planned activities, including hemodynamic assessment, ultrasound monitoring, and clinical data collection, are performed as part of the routine care of critically ill patients in the Intensive Care Unit, using equipment, supplies, and human resources already available at the participating hospitals.

Therefore, the execution of the study does not generate additional costs for the institutions or for the patients involved.

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APPENDIX 1

Functional Maneuvers for the Assessment of Ultrafiltration Tolerance

(Sedated and Mechanically Ventilated Patients)

A. Passive Leg Raising (PLR)

Physiological Rationale

Passive leg raising (PLR) is a reversible “autotransfusion” maneuver that mobilizes venous blood from the lower limbs and the splanchnic venous reservoir toward the intrathoracic compartment, transiently increasing cardiac preload without fluid administration.

In sedated and mechanically ventilated patients, PLR maintains its physiological validity and offers the additional advantage of eliminating interference from muscular effort and spontaneous breathing, allowing a more reproducible assessment of venous return and cardiac output.

Standardized Procedure (PLR from Semi-Recumbent Position)

1. Baseline Conditions

- Sedated patient under controlled mechanical ventilation
- Semi-recumbent position with head of bed elevated at approximately 45°
- Stable vasopressor dose and ventilatory parameters for at least 5 minutes prior to the maneuver

2. Maneuver Execution

- Simultaneous lowering of the trunk to the supine position
- Passive elevation of both lower limbs to approximately 45°, performed by nursing staff, without active patient participation
- The positional transition should be smooth and continuous, avoiding nociceptive stimuli

3. Hemodynamic Assessment

- Baseline recording of hemodynamic variables
- Measurement of aortic velocity–time integral (VTI), cardiac index, or another cardiac output parameter between 30 and 90 seconds after positional change
- A significant increase in cardiac output will be interpreted as preload dependence

4. Reversibility

- Return the patient to baseline position, confirming reversal of induced hemodynamic changes

Specific Safety Considerations

- PLR is particularly safe in sedated and mechanically ventilated patients, as it avoids voluntary muscle activation

- Do not perform the maneuver in the presence of:
    - Uncontrolled intracranial hypertension
    - Spinal instability
    - Known deep vein thrombosis
    - Significant increase in intra-abdominal pressure

B. Sitting Maneuver (Partial Upright Positioning in Sedated Patients)

Physiological Rationale

The postural change from a supine or semi-recumbent position to a sitting position induces gravitational redistribution of blood volume, shifting blood from the intrathoracic compartment to dependent venous compartments.

In sedated and mechanically ventilated patients, this phenomenon occurs passively and predictably, leading to a reduction in venous return, stroke volume, and potentially cardiac output, even in the absence of arterial hypotension.

From a pathophysiological perspective, this maneuver can be considered the functional opposite of PLR, simulating a controlled acute reduction in central blood volume, analogous to the initial effect of net ultrafiltration.

Proposed Safe Sitting Procedure (Progressive Verticalization)

Given the exploratory nature of this maneuver in the CRRT setting, it will be applied under a conservative and strictly supervised protocol.

1. Patient Selection

- Sedated patient under mechanical ventilation
- Absence of overt hemodynamic instability
- Stable vasopressor dose
- No orthopedic, neurological, or respiratory contraindications

2. Baseline Conditions

- Patient in supine or semi-recumbent position (30–45°)
- Baseline recording of blood pressure, heart rate, cardiac output parameters, and peripheral perfusion

3. Maneuver Execution

- Progressive elevation of the trunk using an articulated bed to a near-sitting position (approximately 60–70°), with lower limbs in a dependent position
- The maneuver will be performed gradually under medical and nursing supervision
- Maximum duration: 2–3 minutes

4. Assessment During the Maneuver

- Continuous monitoring of blood pressure and heart rate
- Evaluation of VTI, cardiac index, or other available hemodynamic parameters
- Assessment of peripheral perfusion (capillary refill time, mottling score, PPI)

5. Immediate Interruption Criteria

- Significant hypotension or abrupt drop in blood pressure

- Increased vasopressor requirements
- Onset or worsening of signs of peripheral hypoperfusion

6. Return to Baseline Position

- Immediate return to baseline position if interruption criteria are met or after completion of the observation period

APPENDIX 2

Measurement Schedule (0 to 24-hour window)

T0 (Baseline: before initiation of UF^{NET}) – "Comprehensive assessment"

1) Context and treatment (to be recorded)

- Prescribed UF^{NET} (mL/kg/h), prior cumulative fluid balance, urine output
- Ventilation (mode, PEEP), sedation, temperature
- Vasopressors/inotropes: dose + VIS

2) Macrohemodynamics

- MAP, systolic arterial pressure (SAP), heart rate (HR), pulse pressure (PP), PAD/HR ratio (DSI)
- (If available) $ScvO_2$ / SvO_2

3) Advanced hemodynamics

- Cardiac output / cardiac index and/or VTI (echocardiography or monitor-based)
- SVV/PPV (if under controlled ventilation and monitor available)
- Dynamic arterial elastance (if feasible)

4) Peripheral perfusion

- Capillary refill time (CRT)
- Mottling score
- Peripheral perfusion index (PPI), if available

5) Ultrasound

- Complete VEXUS assessment (IVC + venous Doppler as per protocol)
- Lung ultrasound

6) Baseline biomarkers/laboratory tests

- Lactate
- Albumin
- Ionized calcium
- BNP/NT-proBNP (if available)

7) Functional maneuvers (pre-UFNET only)

- PLR (if feasible) and/or sitting maneuver (if feasible)

T2 (2 hours)

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI
- CI/CO or VTI
- VEXUS
- UF^{NET} rate

T4 (4 hours) – same as T2

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI
- CI/CO or VTI
- VEXUS
- UF^{NET} rate

T6 (6 hours) – "end of early phase"

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI
- CI/CO or VTI
- VEXUS
- Ionized calcium
- UF^{NET} rate

Extended Phase (every 6 hours up to 24 hours)

T12

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI

- CI/CO or VTI
- VEXUS
- Ionized calcium
- UF^{NET} rate
- 12-hour cumulative fluid balance

T18

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI
- CI/CO or VTI
- VEXUS
- Ionized calcium
- UF^{NET} rate

T24

- MAP/SAP/HR/PP/DSI + vasopressors (dose, VIS)
- Lactate
- CRT + mottling + PPI
- CI/CO or VTI
- VEXUS
- Ionized calcium
- Lung ultrasound
- UF^{NET} rate

+ “24-hour assessment”:

- 24-hour cumulative fluid balance, achieved UF^{NET}, therapy interruptions, rescue interventions (fluids/vasopressors)
- (If feasible) BNP/NT-proBNP

“Triggers” (off-schedule assessments)

Whenever any ultrafiltration intolerance criterion occurs (hypotension, increased vasopressor requirement, deterioration of peripheral perfusion, lactate increase, reduction/interruption of UF^{NET}), an abbreviated assessment set should be recorded immediately:

- MAP/SAP/HR/PP/DSI + change in vasopressors
- Lactate
- CRT / mottling / PPI
- CI/CO or VTI
- VEXUS

APPENDIX 3

Vasoactive-Inotropic Score (VIS)

The Vasoactive-Inotropic Score (VIS) quantifies the intensity of vasoactive and inotropic support using a standardized formula. It will be calculated at each measurement time point using continuous infusion doses:

VIS = dopamine (µg/kg/min) + dobutamine (µg/kg/min) + 100 × epinephrine (µg/kg/min) + 100 × norepinephrine (µg/kg/min) + 10,000 × vasopressin (U/kg/min) + 10 × milrinone (µg/kg/min).

VIS = dopamine dose (µg/kg/min) +
dobutamine dose (µg/kg/min) +
100 x epinephrine dose (µg/kg/min) +
10 x milrinone dose (µg/kg/min) +
10,000 x vasopressin dose (U/kg/min) +
100 x norepinephrine dose (µg/kg/min)

APPENDIX 4. DEFINITION OF VARIABLES RECORDED IN THE CRF

Variables will be recorded at two clearly differentiated time points:

1. **ICU admission (Baseline ICU):** demographic characteristics, comorbidities, and initial severity.

2. **Initiation and during CRRT/UF^{NET} (T0-UF^{NET}):** clinical, hemodynamic, perfusion, fluid status, and support variables at the physiologically relevant time point for ultrafiltration tolerance.

A. VARIABLES RECORDED AT ICU ADMISSION

Demographic Data

- **ICU admission date:** calendar date (DD-MM-YYYY)
- **ICU discharge date:** date recorded in the medical record as transfer or death (DD-MM-YYYY)
- **Age at ICU admission:** years
- **Biological sex:**
    - Female = 0
    - Male = 1

Comorbidities (previous history)

- **Arterial hypertension (HTN):** documented history or chronic treatment
    - No = 0 | Yes = 1
- **Type 2 diabetes mellitus (T2DM):** documented history or prior treatment
    - No = 0 | Yes = 1

- **Chronic kidney disease (CKD):** eGFR <60 mL/min/1.73 m² prior to admission
  - No = 0 | Yes = 1
- **Heart failure:** prior clinical or echocardiographic diagnosis
  - No = 0 | Yes = 1
- **Chronic liver disease:** clinical or imaging-based diagnosis
  - No = 0 | Yes = 1
- **Cerebrovascular disease:** documented history
  - No = 0 | Yes = 1
- **Peripheral vascular disease:** documented history
  - No = 0 | Yes = 1
- **Smoking status:**
  - Never smoker = 0
  - Former or current smoker = 1

Anthropometry

- **Weight at ICU admission:** kg (1 decimal)
- **Height:** meters (1 decimal)
- **BMI:** kg/m² (1 decimal)

Admission Context

- **Primary ICU diagnosis:** main diagnosis (to be coded)
- **SOFA score at ICU admission:** worst value within the first 24 hours

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B. VARIABLES RECORDED AT INITIATION/DURING CRRT / UF^{NET}

Variables recorded immediately prior to CRRT/UFNET initiation should ideally be obtained within ±1 hour (maximum 6 hours prior).

Temporal Context

- **Days from ICU admission to CRRT initiation:** continuous variable (days)
- **Primary indication for CRRT:** volume overload / uremia / acidosis / hyperkalemia / oliguria-anuria / others (to be coded)

Severity and Support

- **SOFA at CRRT initiation (SOFA-CRRT):** worst values within the previous 6 hours
- **Invasive mechanical ventilation at CRRT initiation:**
  - No = 0 | Yes = 1

Vasoactive and Inotropic Support

- **Use of vasopressors at CRRT initiation:**
  - No = 0 | Yes = 1
- **Vasopressor doses (µg/kg/min):**
  - Norepinephrine
  - Epinephrine
  - Vasopressin (U/min)
- **Use of inotropes:**
  - No = 0 | Yes = 1
- **Inotrope doses:**
  - Dobutamine (µg/kg/min)
  - Milrinone (µg/kg/min)
- **VIS score (Vasoactive–Inotropic Score):** calculated using standard formula
- **High-dose vasoactive support:** defined as norepinephrine >0.3 µg/kg/min
  - No = 0 | Yes = 1

Baseline Laboratory Values (pre-CRRT)

- Hemoglobin (g/dL)
- Lactate (mmol/L)
- Albumin (g/dL)
- Plasma sodium (mmol/L)
- Plasma potassium (mmol/L)
- Total calcium (mg/dL)
- Ionized calcium (mmol/L), if available
- Plasma phosphorus (mg/dL)
- Hypophosphatemia: phosphorus <2.5 mg/dL
    - No = 0 | Yes = 1

Hemodynamics and Peripheral Perfusion

- MAP, SAP, DAP (mmHg)
- Heart rate (bpm)
- Pulse pressure (PP): SAP − DAP
- Diastolic shock index (DSI): HR / DAP
- Capillary refill time (CRT) (seconds)
- Mottling score (0–5)
- Peripheral Perfusion Index (PPI)

Ultrasound Variables

Cardiac echocardiography:

- Left ventricular ejection fraction (%)
- LVOT VTI (cm)
- Cardiac index (L/min/m²)
- IVC diameter and collapsibility
- E/e′ ratio (if available)

Venous ultrasound – VExUS:

- Hepatic vein flow pattern
- Portal vein flow pattern

- Intrarenal venous flow pattern
- VExUS grade (0–3)

C. FLUID VARIABLES

C1. Fluid Status Before CRRT Initiation

- **Pre-CRRT cumulative fluid balance (mL):** Σ (inputs − outputs) from ICU admission to 1 hour before CRRT
- **Fluid overload at CRRT initiation (FO%, %):**
  FO% = [Σ (inputs − outputs) in liters / reference weight (kg)] × 100
- **Reference weight:** ICU admission weight (or earliest recorded)

C2. Fluid Balance 0–24 h from CRRT Initiation

- **Total inputs 0–24 h (mL):** IV fluids, blood products, nutrition, infusions, etc.
- **Total outputs 0–24 h (mL):** urine + drains + GI/insensible losses + UF^{NET}
- **Net fluid balance 0–24 h (mL):** inputs − outputs
- **Cumulative balance at 24 h (mL):** pre-CRRT balance + net 0–24 h balance

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C3. UF^{NET}, Targets, and "Fluid Gap"

- **UF^{NET}:**
  - Prescribed rate: mL/kg/h
  - Achieved rate: mL/kg/h
- **Fluid balance goal (FBGoal, mL):** clinical target for 24-hour fluid balance
- **Achieved balance (FBAchieved, mL):** actual balance achieved
- **Fluid gap (%FBGap):**
  %FBGap = [(FBGoal − FBAchieved) / FBGoal] × 100
  Note: if FBGoal is negative, use |FBGoal| as denominator.
- **Reduction/suspension of UF^{NET} due to intolerance:**
  - No = 0 | Yes = 1

Event Defining Ultrafiltration Intolerance

Record one or more of the following (non-mutually exclusive):

- Clinically significant hypotension (hemodynamic)
- Increased vasopressor/inotropic requirements (hemodynamic)
- Peripheral perfusion deterioration (prolonged CRT, increased mottling, decreased PPI)
- Evidence of tissue hypoperfusion (lactate increase per protocol)

Classification of UF^{NET} Intolerance Mechanism

- Hemodynamic
- Peripheral perfusion
- Metabolic (lactate)
- Mixed

CRRT Variables

- CRRT modality: CVVH / CVVHD / CVVHDF
- Prescribed UF^{NET} rate: mL/kg/h
- Achieved UF^{NET} rate: mL/kg/h (24 h)
- Prescribed CRRT dose: mL/kg/h (effluent)

Outcomes

- ICU length of stay (LOS ICU): days
- ICU mortality: No = 0 | Yes = 1
- Cause of ICU mortality: free text (to be coded)
- 30-day mortality: No = 0 | Yes = 1