Additional file 1: Supplementary Tables and Figures

Supplementary Table 1. High-risk criteria for fluid-induced harm

Medical History	Clinical Signals
Previous Cardiomyopathy, pulmonary disease, or kidney disease	New onset diastolic or systolic cardiac dysfunction
> 65 years	Acute kidney injury
Suspected or diagnosed pneumonia	Baseline CVP > 10 mmHg
Suspected or diagnosed intra-abdominal hypertension	Capillary leak index[a] >60

Abbreviations: CVP, central venous pressure.
[a]Capillary leak index was defined as C-reactive protein (milligrams per deciliter) over albumin (grams per liter) ratio, multiplied by 100.

Supplementary Table 2. Exclusion criteria

Exclusion criteria
Pregnancy
Do-not-resuscitate status
Acute coronary syndrome
Active bleeding
Severe concomitant acute respiratory distress syndrome (PaO_2:FiO_2 ratio <100)
Prone positioning
Anticipated surgery
Renal replacement therapy in the next 6 hours
Refractory shock at the attending physician's discretion
Body mass index >40 kg/m^2
Inadequate echocardiographic window

Abbreviations: PaO_2:FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

Supplementary Table 3. Data availability (number of participants with available data) by variable and timepoint

	0 h	6 h	24 h
Hemodynamics			
Heart rate	17/15	17/16	14/14
Mean arterial pressure	17/15	17/16	14/14
Pulse pressure	17/16	17/16	14/13
Cardiac output	15/15	13/14	10/10
Stroke volume	11/15	12/13	11/9
Ventilation / oxygenation			
PaO_2:FiO_2	18/17	18/17	14/14
PEEP	18/16	18/16	13/14
Plateau pressure	18/16	16/16	12/13
FiO_2	18/17	18/17	14/14
Organ-injury biomarkers			
Creatinine	14/15	14/15	13/13
NT-proBNP	14/15	14/15	13/13
hs-cTnT	14/15	14/15	13/13
NGAL	14/15	14/15	13/13
Cystatin C	14/15	14/15	13/13
Perfusion			
Lactate	18/17	18/16	12/11
CRT	18/16	18/16	14/14
$ScvO_2$	17/16	17/16	11/14
Diuresis	—	16/15	12/11
Fluid-intolerance signals			
CVP	15/16	16/14	10/12
LUS	NA[a]/12	16/13	14/12
VExUS	NA[a]/11	15/14	13/11
E/lateral e′	NA[a]/10	18/12	14/11
Other			
Norepinephrine dose	18/17	16/16	14/14
Fluid balance	—	13/14	12/11

Abbreviations: PaO_2:FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; NGAL, plasma neutrophil gelatinase-associated lipocalin; CRT, capillary refill time; $ScvO_2$, central venous oxygen saturation; CVP, central venous pressure; LUS, lung ultrasound score; VExUS, Venous Excess Ultrasound; E/lateral e′ ratio, ratio of early diastolic mitral inflow velocity to early diastolic lateral mitral annular velocity.

Values are the number of participants with available data (standard care/intervention). Total analyzed: 18 standard care and 17 intervention.

—, not applicable (diuresis and fluid balance are cumulative measures without a baseline value).

[a]Baseline ultrasound was not performed in the standard care arm by design, to avoid influencing bedside decisions (NA, not assessed).

Supplementary Table 4. Oxygenation, ventilatory settings, and cardiac output at baseline, 6 hours, and 24 hours

	Standard care	Intervention	Difference (95% CI)
PaO_2, mmHg			
Baseline	101.0 [82.0-123.0]	89.2 [78.0-114.0]	-7.5 (-29.0 to 11.0)
6 h	86.8 [73.6-112.0]	89.5 [75.0-117.0]	3.2 (-12.6 to 21.0)
24 h	82.0 [73.0-86.2]	91.3 [87.6-115.0]	11.3 (-5.4 to 28.8)
FiO_2, %			
Baseline	40 [30-50]	40 [30-50]	0 (-10 to 10)
6 h	40 [35-60]	30 [30-40]	-5 (-12 to 0)
24 h	40 [30-40]	32.5 [30-40]	0 (-10 to 5)
PaO_2:FiO_2			
Baseline	271.8 [233.3-343.3]	260.0 [187.5-286.7]	-18.1 (-87.8 to 40.0)
6 h	236.2 [177.5-280.0]	286.7 [245.0-373.3]	60.8 (0.8 to 128.5)
24 h	224.2 [162.0-287.3]	275.4 [235.3-317.7]	51.4 (-11.3 to 122.8)
PEEP, cmH_2O			
Baseline	6 [5-8]	7.5 [5.5-8]	0.0 (0.0 to 2.0)
6 h	6 [6-8]	8 [6-8]	1.0 (-1.0 to 2.0)
24 h	6 [5-8]	7 [5-8]	0.0 (0.0 to 2.0)
Plateau pressure, cmH_2O			
Baseline	18 [16-21]	18.5 [16-20.5]	0.0 (-3.0 to 2.0)
6 h	18 [16-21.5]	18.5 [17-20]	0.0 (-3.0 to 2.0)
24 h	17.5 [15-20.5]	18 [16-20]	0.0 (-3.0 to 4.0)
Cardiac output, L/min			
Baseline	5.5 [4.7-7]	5.5 [4.6-6.8]	-0.1 (-1.2 to 0.9)
6 h	5.8 [5.3-8.7]	4.3 [3.9-6.0]	-1.6 (-3.6 to -0.2)
24 h	5.7 [5.4-7.1]	5.1 [3.4-5.7]	-1.0 (-2.5 to 0.6)

Abbreviations: PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; PaO_2:FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PEEP, positive end-expiratory pressure.

Values are median [interquartile range]. Denominators vary by variable and timepoint owing to missing data (see Supplementary Table 3).

Supplementary Table 5. Post hoc sensitivity analyses for the primary outcome (0–6 hour change in PaO_2:FiO_2)

Analysis	No. analyzed (standard care/intervention)	Between-group difference (95% CI)
Restricted (subgroup) analyses		
FiO_2 change ≤10 percentage points	15/14	70.9 (41.5 to 94.3)
No decrease in FiO_2	10/8	70.8 (32.5 to 112.7)
No increase in PEEP	14/13	69.3 (39.2 to 93.7)
FiO_2 change ≤10 points and no increase in PEEP	12/12	64.5 (33.3 to 87.2)
Adjusted linear regression models		
Adjusted for baseline PaO_2:FiO_2	35	80.8 (48.4 to 113.1)
Adjusted for baseline PaO_2:FiO_2, FiO_2 and PEEP at 6 h	35	64.0 (31.2 to 96.9)
Adjusted for baseline PaO_2:FiO_2 and cardiac output at 6 h	27	85.7 (38.0 to 133.4)
Adjusted for baseline PaO_2:FiO_2, FiO_2, PEEP and cardiac output at 6 h	27	73.9 (30.1 to 117.8)
Same model with heteroskedasticity-robust (HC3) standard errors	27	73.9 (17.5 to 130.3)

Abbreviations: FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; PaO_2:FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.
All analyses were post hoc and exploratory. For restricted analyses, differences are presented as Hodges–Lehmann median differences (intervention minus standard care) with distribution-free 95% confidence intervals. For the adjusted models, values are regression coefficients for treatment group with 95% confidence intervals. The number analyzed varies across analyses because of missing data, particularly for cardiac output. These analyses were not prespecified and are reported to assess whether the primary signal persisted after accounting for ventilatory settings and cardiac output.

Supplementary Table 6. Additional exploratory outcomes at 6 hours

	Standard care	Intervention	Between-group difference (95% CI)
Hemodynamics			
Pulse pressure, median [IQR], mmHg	48 [40-55]	48 [36-59.5]	1.0 (-10.0 to 12.0)
Stroke volume, median [IQR], mL/beat	66.1 [46.6-82.6]	51.4 [41.2-78.1]	-6.2 (-26.9 to 14.5)
Mechanical ventilation			
Plateau pressure, median [IQR], cmH_2O	18 [16-21.5]	18.5 [17-20]	0.0 (-3.0 to 2.0)
Interventions			
Other vasopressors[a], No. (%)	8 (50.0)	7 (41.2)	
Organ-injury biomarkers			
ΔCreatinine (6h-0h), median [IQR], mg/dL	-0.08 [-0.2 to 0.06]	-0.04 [-0.25 to 0.25]	0.04 (-0.23 to 0.32)
Creatinine, median [IQR], mg/dL	2.48 [1.31-3.32]	2.38 [1.56-3.76]	-0.07 (-0.95 to 1.07)
ΔNT-proBNP (6h-0h), median [IQR], ng/L	145 [-3278 to 1745]	162 [-1730 to 5126]	440 (-2511 to 4428)
NT-proBNP, median [IQR], ng/L	21565 [4631-34212]	11460 [1382-28065]	-4983 (-26200 to 5692)
Δhs-cTnT (6h-0h), median [IQR], ng/L	5.3 [-2.1 to 33.2]	0.8 [-1.7 to 27.3]	-0.1 (-20.8 to 29.3)
hs-cTnT, median [IQR], ng/L	82.3 [44.4-133.8]	68.3 [19.2-281.1]	-6.5 (-58.5 to 165.4)
ΔNGAL (6h-0h), median [IQR], ng/mL	-83.5 [-112 to 28]	-26 [-307 to 165]	30 (-193 to 219)
NGAL, median [IQR], ng/mL	1080 [706-1521]	1566 [623-2861]	309 (-507 to 1366)
ΔCystatin C (6h-0h), median [IQR], mg/L	0.01 [-0.16 to 0.19]	0.03 [-0.28 to 0.1]	0.00 (-0.35 to 0.23)
Cystatin C, median [IQR], mg/L	2.4 [1.7-3.1]	2.8 [1.1-3.8]	0.05 (-1.05 to 1.22)
Perfusion			
Lactate, median [IQR], mmol/L	4.1 [2.3-8.9]	3.2 [2.7-4.5]	-0.6 (-3.5 to 0.8)
$ScvO_2$, median [IQR], %	78 [74.5-80.5]	74 [69.6-78]	-4 (-9 to 2)
Diuresis, median [IQR], mL	180 [30-363]	363 [70-430]	85 (-80 to 310)

Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; NGAL, plasma neutrophil gelatinase-associated lipocalin; $ScvO_2$, central venous oxygen saturation.

Values are median [interquartile range], measured at 6 hours unless otherwise indicated. Between-group differences are Hodges–Lehmann median differences (intervention minus standard care) with distribution-free 95% confidence intervals. Denominators vary by variable owing to missing data (see Supplementary Table 3).

[a]At 6 hours, other vasoactive drugs included vasopressin (3 standard care, 6 intervention), epinephrine (5 and 1), milrinone (1 and 1), and dobutamine (0 and 1); no patient received phenylephrine. Values for additional vasoactive drugs are proportions of participants with data available at 6 hours (16 standard care, 17 intervention).

Supplementary Table 7. Prespecified outcomes and measures at hour 24

	Standard care	Intervention	Between-group difference (95% CI)
Hemodynamics			
Heart rate, median [IQR], beats/min	91 [85-99]	78.5 [69-89]	-12.0 (-23.0 to -2.0)
Mean arterial pressure, median [IQR], mmHg	75.5 [71-83]	74 [68-80]	-3.0 (-10.0 to 5.0)
Pulse pressure, median [IQR], mmHg	57.5 [49-62]	47 [44-53]	-5.0 (-14.0 to 7.0)
Cardiac output, median [IQR], L/min	5.7 [5.4-7.1]	5.1 [3.4-5.7]	-1.0 (-2.5 to 0.6)
Stroke volume, median [IQR], mL/beat	54.6 [51.1-73.1]	57 [47.9-59]	-3.0 (-23.2 to 13.6)
Mechanical ventilation			
PEEP, median [IQR], cmH_2O	6 [5-8]	7 [5-8]	0.0 (0.0 to 2.0)
Plateau Pressure, median [IQR], cmH_2O	17.5 [15-20.5]	18 [16-20]	0.0 (-3.0 to 4.0)
FiO_2, median [IQR], %	40 [30-40]	32.5 [30-40]	0.0 (-10.0 to 5.0)
Interventions			
NE dose, median [IQR], µg/kg/min	0.22 [0.11-0.55]	0.28 [0.13-0.38]	0.00 (-0.20 to 0.16)
Other vasopressors, No. (%)	5 (35.7)	4 (30.8)	-4.9 (-38.1 to 26.3)
Fluid balance, median [IQR], mL	1918 [562-3236]	1100 [175-2449]	-630 (-2231 to 954)
Organ function			
ΔPaO_2:FiO_2 (24h-0h), median [IQR]	-59.1 [-84 to -1.9]	42.2 [-32.1 to 73]	79.8 (7.8 to 135.3)
ΔCreatinine (24h-0h), median [IQR], mg/dL	-0.29 [-0.42 to -0.12]	0.07 [-0.25 to 0.67]	0.35 (-0.04 to 0.96)
Creatinine, median [IQR], mg/dL	2.05 [1.43-2.94]	2.28 [1.39-3.88]	0.39 (-0.74 to 1.83)
ΔNT-proBNP (24h-0h), median [IQR], ng/L	-514 [-7390 to 1288]	619 [-753 to 5846]	1786 (-7328 to 9536)
NT-proBNP, median [IQR], ng/L	14070 [5290-58280]	7725 [942-20511]	-4848 (-32901 to 2435)
Δhs-cTnT (24h-0h), median [IQR], ng/L	-1.5 [-16 to 28.1]	-0.9 [-32.4 to 8.6]	-6.0 (-110.3 to 36.1)
hs-cTnT, median [IQR], ng/L	67.4 [33.7-225.5]	55.6 [37.6-275.9]	3.5 (-112.0 to 185.1)
ΔNGAL (24h-0h), median [IQR], ng/mL	-178 [-279 to -26]	-12 [-489 to 366]	166 (-274 to 519)
NGAL, median [IQR], ng/mL	698 [528-1422]	884 [613-2567]	194 (-538 to 1277)
ΔCystatin C (24h-0h), median [IQR], mg/L	0.02 [-0.36 to 0.15]	0.07 [-0.16 to 0.3]	0.15 (-0.35 to 0.84)
Cystatin C, median [IQR], mg/L	2.1 [1.5-2.9]	2.6 [1.3-4.2]	0.36 (-0.89 to 1.72)
Perfusion			
ΔLactate, median [IQR], mmol/L	-1.8 [-4.44 to -0.88]	-1.0 [-2.5 to -0.4]	0.85 (-1.50 to 3.40)
Lactate, median [IQR], mmol/L	1.89 [1.55-2.33]	2.1 [1.8-3.4]	0.20 (-0.52 to 0.95)
ΔCRT, median [IQR], s	-1 [-3 to 0]	-1 [-2 to 0]	0.0 (-1.5 to 2.0)
CRT, median [IQR], s	3 [2-4]	2 [2-3]	-1.0 (-2.0 to 1.0)
$ScvO_2$, median [IQR], %	76.4 [68.8-79.3]	71.7 [67-77.4]	-3.2 (-10.1 to 3.9)
Fluid-intolerance signals			
LUS, median [IQR]	5 [2-8]	3.5 [0-7.5]	-2.0 (-5.0 to 3.0)
CVP, median [IQR], mmHg	7.5 [4-10]	10 [9-14.5]	3.5 (0.0 to 7.0)
VExUS, median [IQR]	0 [0-0]	0 [0-1]	N/A
VExUS Grade, No. (%) Grade 0	 11 (84.6)	 8 (72.7)	N/A

Grade 1 Grade 2 Grade 3	1 (7.7) 1 (7.7) 0 (0)	1 (9.1) 2 (18.2) 0 (0)	
E/lateral e′ ratio, median [IQR]	7.1 [5.8-8.5]	7.73 [4.09-11.67]	0.60 (-2.72 to 4.31)

Abbreviations: PEEP, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; NE, norepinephrine; PaO_2:FiO_2, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-cTnT, high-sensitivity cardiac troponin T; NGAL, plasma neutrophil gelatinase-associated lipocalin; CRT, capillary refill time; $ScvO_2$, central venous oxygen saturation; LUS, lung ultrasound score; CVP, central venous pressure; VExUS, Venous Excess Ultrasound; E/lateral e′ ratio, ratio of early diastolic mitral inflow velocity to early diastolic lateral mitral annular velocity. N/A: not available.

Denominators vary across 24-hour variables because of deaths and missing data; percentages and categorical distributions were calculated from patients with available data at 24 hours. Per-variable data availability at each timepoint is reported in Supplementary Table 3.

Between-group differences are Hodges–Lehmann median differences (intervention minus standard care) with distribution-free 95% confidence intervals for continuous variables, and risk differences (percentage points) with 95% confidence intervals for binary variables.

Supplementary Table 8. Long-term outcomes

	Standard care	Intervention
Day-7 AKI, No. (%)[†]	12 (80)	12 (75)
Vasopressor free days[a], median [IQR]	0 [0-23]	10 [0-24]
Renal replacement therapy free days[b], median [IQR]	0 [0-28]	26 [0-28]
Mechanical ventilation free days[c], median [IQR]	0 [0-20]	7 [0-15]
Organ dysfunction-free days[d], median [IQR]	0 [0-20]	7 [0-15]
28-day mortality, No. (%)	10 (55.6)	8 (47.1)

Abbreviations: AKI, acute kidney injury.

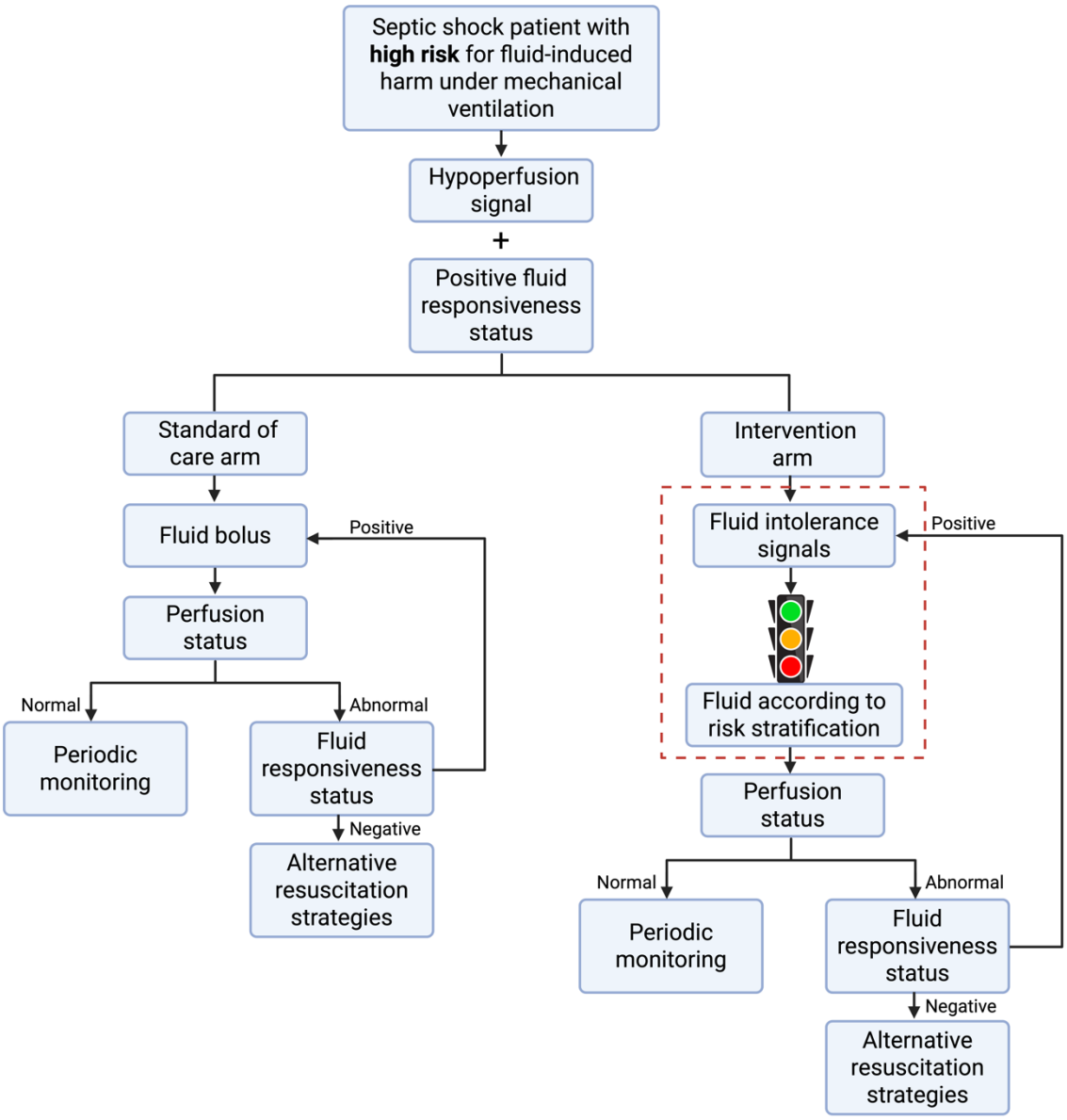
[†]Day-7 AKI was a post hoc exploratory outcome, assessed in patients with available 7-day data (n = 15 standard care, n = 16 intervention); 4 patients (3 standard care, 1 intervention) had missing 7-day data and were excluded from this calculation. All other outcomes were available for the 35 analyzed patients.

[a]Vasopressor free days defined as the number of days alive and free of vasopressor through day 28 after enrollment.

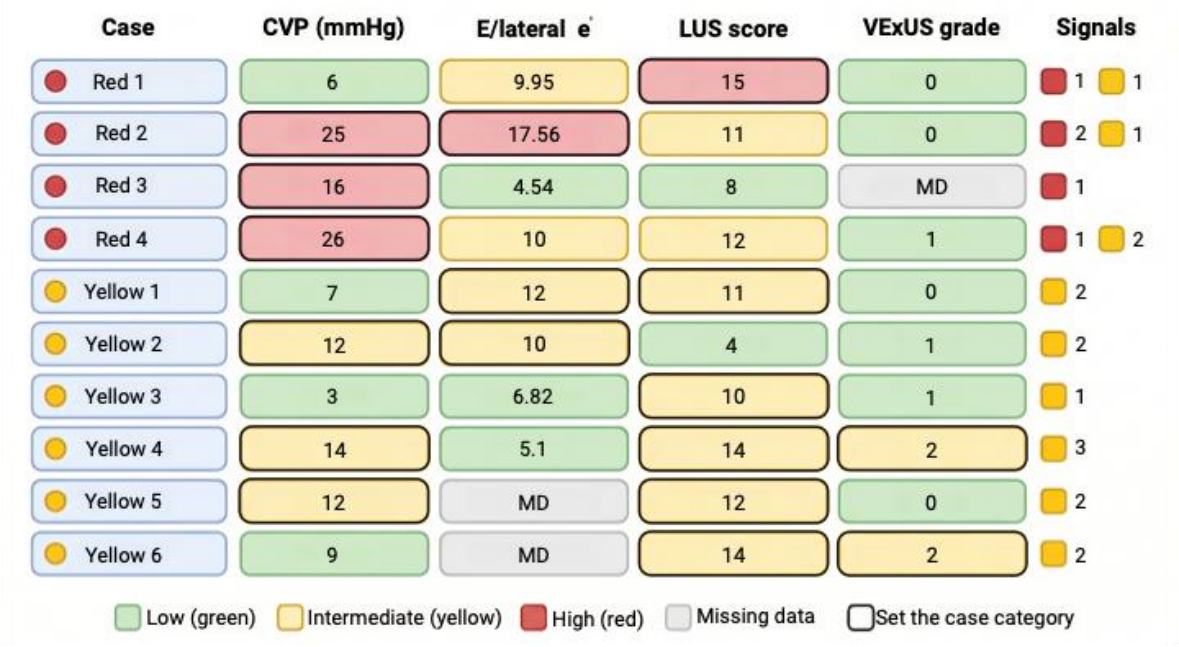
[b]Renal replacement therapy free days defined as the number of days alive and free of renal replacement therapy through day 28 after enrollment.

[c]Mechanical ventilation free days defined as the number of days alive and free of mechanical ventilation through day 28 after enrollment.

[d]Organ dysfunction-free days defined as the number of days alive and simultaneously free of vasopressor, mechanical ventilation, and renal replacement therapy support through day 28 after enrollment.



Supplementary Figure 1. Standard and intervention resuscitation protocols.



Supplementary Figure 2. Baseline fluid-intolerance signals by domain in intervention-group participants classified as intermediate (yellow) and high (red) risk. Each row represents one participant; columns show the four intolerance domains (CVP, E/lateral e′, LUS, and VExUS), with the measured value and the domain-level traffic-light category indicated by cell color (green, low; yellow, intermediate; red, high; gray, missing data). A bold black outline marks the domain that set the overall case category (the worst, highest-risk domain). The "Signals" column summarises the number of red and yellow domains per case. Values are baseline measurements obtained immediately before the first protocol bolus. Only the 10 participants classified as yellow (n=6) or red (n=4) are shown; the 6 green-category participants (all domains green) and 1 participant with missing classification are not displayed. **Abbreviations:** CVP, central venous pressure; E/lateral e′, ratio of early diastolic mitral inflow velocity to early diastolic lateral mitral annular velocity; LUS, Lung ultrasound score; VExUS, Venous Excess Ultrasound; MD, missing data.

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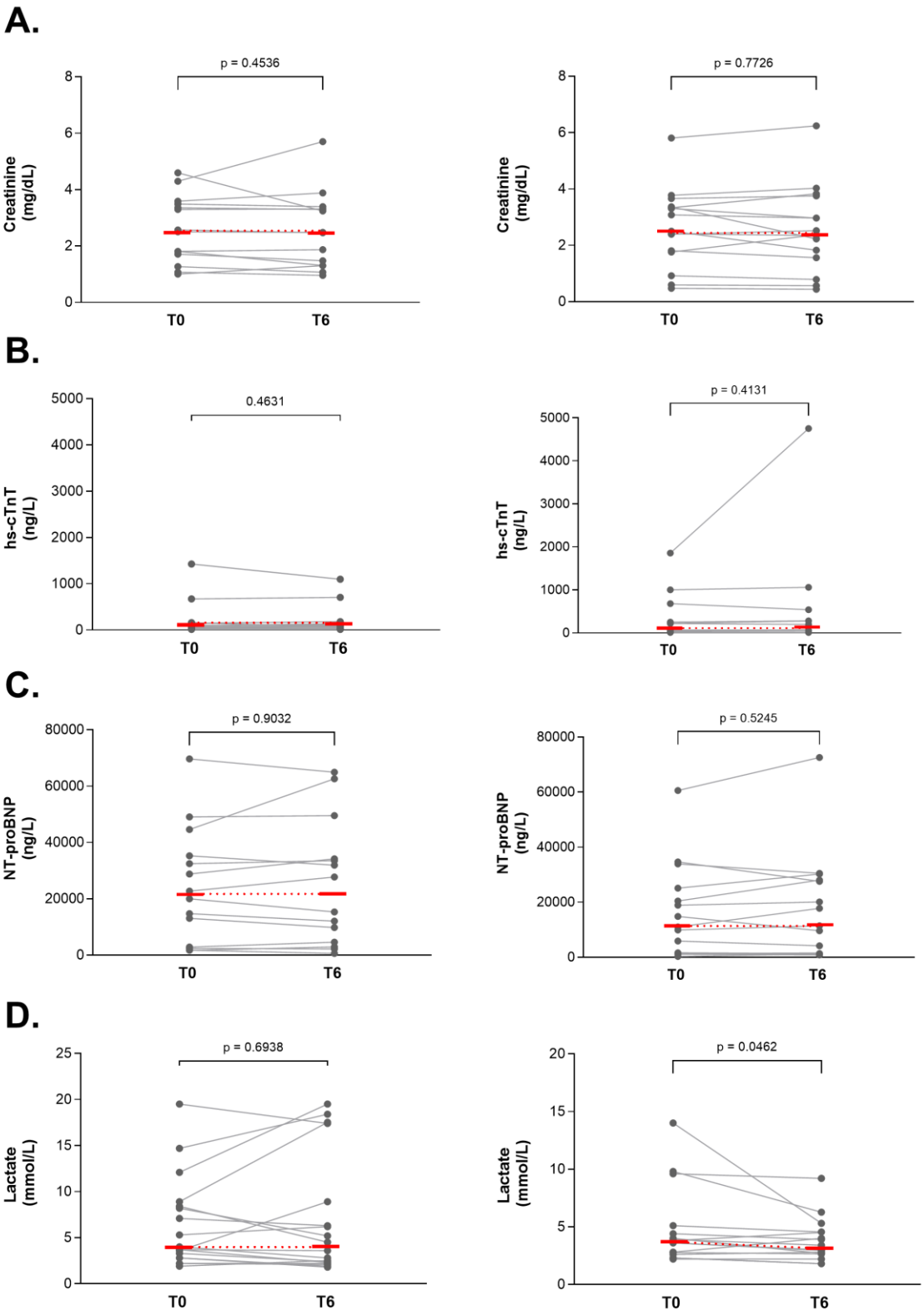
A.
p = 0.4536
Creatinine (mg/dL)
0
2
4
6
8
T0
T6
p = 0.7726
Creatinine (mg/dL)
0
2
4
6
8
T0
T6
B.
0.4631
hs-cTnT (ng/L)
0
1000
2000
3000
4000
5000
T0
T6
p = 0.4131
hs-cTnT (ng/L)
0
1000
2000
3000
4000
5000
T0
T6
C.
p = 0.9032
NT-proBNP (ng/L)
0
20000
40000
60000
80000
T0
T6
p = 0.5245
NT-proBNP (ng/L)
0
20000
40000
60000
80000
T0
T6
D.
p = 0.6938
Lactate (mmol/L)
0
5
10
15
20
25
T0
T6
p = 0.0462
Lactate (mmol/L)
0
5
10
15
20
T0
T6

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Supplementary Figure 3. Within-group trajectories during the 6-hour protocol window. (A) Creatinine (mg/dL), (B) hs-cTnT (ng/L), (C) NT-proBNP (ng/L), (D) Lactate (mmol/L) at baseline (T0) and 6 hours (T6), shown separately for the standard care and intervention groups. Gray lines connect paired measurements for each participant; red horizontal bars indicate medians, and the red dashed line connects medians. The *p* values correspond to within-group paired comparisons between T0 and T6, obtained from the Wilcoxon signed-rank test. These within-group p values should not be interpreted as evidence of a between-group treatment effect. Per-variable data availability is reported in Supplementary Table 3. **Abbreviations:** hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.