Additional file 2: Supplementary Fluid-Intolerance Signals

Standardized acquisition and scoring protocol for the bedside fluid-intolerance signals

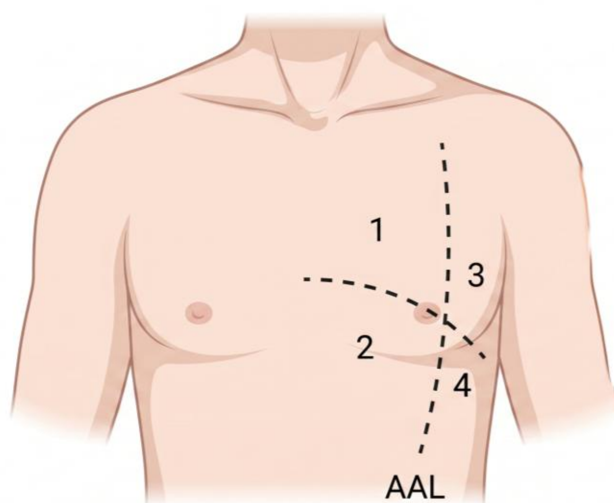
This document details the standardized protocol used to acquire and score the four prespecified fluid-intolerance signals applied as bedside safety limits in the intervention arm: the anterolateral lung ultrasound score (LUS), the Venous Excess Ultrasound (VExUS) grade, the echocardiographic ratio of early diastolic mitral inflow velocity to early diastolic lateral mitral annular velocity (E/lateral e′), and central venous pressure (CVP). All bedside ultrasound assessments were performed by trained study investigators using a Mindray M9 ultrasound system (Mindray Bio-Medical Electronics Co., Shenzhen, China). To minimize interobserver variability, operators underwent protocol-specific training and used standardized scoring worksheets; images and measurements were recorded and, when feasible, archived for quality review.

In the intervention arm, all signals were obtained at baseline, immediately before the first protocol bolus, and reassessed after fluid administration to update the traffic-light risk category before each subsequent bolus. To avoid contaminating bedside decisions, baseline ultrasound fluid-intolerance measures were not obtained in the standard-care arm.

Signal selection followed the pragmatic framework applied in our previous work [1]; signals had to be noninvasive, obtainable at the bedside, and cover complementary physiological domains (pulmonary fluid intolerance, systemic venous congestion, and left-sided filling pressure). Thresholds were selected a priori as safety limits to modulate fluid dosing rather than as diagnostic cut-offs for pulmonary edema or congestion and were anchored to previously published prognostic values. In a cohort of patients with shock, 28-day mortality was substantially higher in the upper two LUS quartiles (scores above approximately 10) than in the lower [2]. VExUS grades 2 and 3 were both associated with subsequent acute kidney injury in the cohort in which the score was developed [3]. For E/lateral e′, the lower bound of 8 corresponds to the conventional lower limit of the diagnostic grey zone for E/e′, below which left-sided filling pressures are generally considered normal, a range originally described in septic patients [4], whereas a lateral E/e′ above 13 is an independent risk factor for left ventricular diastolic dysfunction in septic shock [5]. Because these thresholds were intended to trigger a reduction in fluid dose rather than to establish a diagnosis, we used a lower intermediate threshold for E/lateral e′ (>8) than the single cut-off applied in previous observational work [1]. For CVP, the 12 and 15 mmHg boundaries correspond to the CVP target range recommended for mechanically ventilated patients with septic shock at the time the protocol was designed [6,7], so that values above 15 mmHg exceed that target. A CVP above 12 mmHg has been associated with the highest mortality in septic shock [6] and with impaired microcirculatory blood flow in sepsis [7]; the same threshold was used in our previous work [1]. The dynamic criteria after a fluid bolus were pragmatic protocol choices intended to capture reduced venous compliance rather than thresholds derived from prognostic studies.

1. Anterolateral Lung Ultrasound score (LUS)

Lung aeration was assessed with the patient supine or near-supine using a low-frequency transducer (phased-array or convex), with an eight-zone examination consistent with evidence-based point-of-care LUS recommendations and the protocol applied by Yin et al. [2]. The anterior and lateral chest wall of each hemithorax was divided into four areas, giving eight zones in total: upper anterior (area 1), lower anterior (area 2), upper lateral (area 3), and lower (basal) lateral (area 4) (Additional file Fig. 1). In each zone, the worst aeration pattern observed was recorded and scored from 0 to 3 (Additional file Table 1) [2,8].



Additional file Fig. 1. Eight-zone lung ultrasound examination protocol. Each hemithorax is separated into four quadrants: anterior and lateral zones (separated by the anterior axillary lines), with each one divided into upper and lower portions. Abbreviation: AAL, anterior axillary line.

Additional file Table 1. Aeration pattern and score for LUS

Score	Aeration pattern in the region
0	Lung sliding with A-lines, or fewer than two isolated B-lines.
1	Multiple well-defined B-lines (B1 lines).

2	Multiple coalescent B-lines (B2 lines).
3	Tissue-like pattern with dynamic air bronchograms (lung consolidation).

Zone scores were summed for a total LUS ranging from 0 (fully aerated) to 24 (complete loss of aeration in all eight zones).

Prespecified risk categories (defined a priori): low risk, LUS <10; intermediate risk, LUS 10–14 or a rise of 2 points from baseline; high risk, LUS > 14 or a rise of > 4 points from baseline [2].

2. Venous Excess Ultrasound (VExUS)

Systemic venous congestion was graded from 0 to 3 using the Venous Excess Ultrasound grading system as originally described [3]. The inferior vena cava (IVC) diameter was first assessed in the subxiphoid long-axis view. When the maximum IVC diameter was < 2 cm, the patient was classified as grade 0. When the IVC was ≥ 2 cm (plethoric), the severity of the flow abnormality was evaluated in three venous Doppler signals:

Hepatic vein (pulsed-wave Doppler): normal (systolic [S] wave larger than diastolic [D] wave), mild (S < D, S remaining below baseline), or severe (reversal of the S wave above baseline).

Portal vein: normal (pulsatility fraction < 30%), mild (30–49%), or severe (≥ 50%).

Intrarenal venous Doppler: normal (continuous), mild (biphasic, discontinuous S and D phases), or severe (monophasic, D-only).

The VExUS grade was assigned as: grade 0, IVC < 2 cm; grade 1, IVC ≥ 2 cm with only mild abnormalities; grade 2, IVC ≥ 2 cm with a severe pattern in one of the three veins; grade 3, IVC ≥ 2 cm with severe patterns in two or more veins.

Prespecified risk categories: low risk, grade 0–1; intermediate risk, grade 2; high risk, grade 3 [3].

3. Echocardiographic E/lateral e′ ratio

Transthoracic echocardiography was performed from the apical four-chamber view using a phased-array transducer. Transmitral inflow was recorded with pulsed-wave Doppler, the sample volume positioned at the tips of the mitral leaflets, and the peak early diastolic velocity (E) was measured. Pulsed-wave tissue Doppler imaging was used to record the peak early diastolic velocity of the lateral mitral annulus (lateral e′). The E/lateral e′ ratio was calculated as a noninvasive surrogate of left-sided filling pressure [4,5]. Measurements were averaged over at least three consecutive cardiac cycles (and more in the presence of an irregular rhythm); fusion of the E and A waves was avoided where possible.

Prespecified risk categories: low risk, E/lateral e′ < 8; intermediate risk, 8–13; high risk, > 13 [4,5].

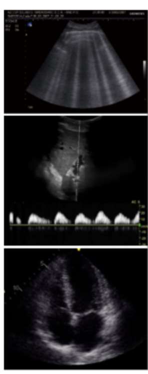
4. Central venous pressure (CVP)

Although not an ultrasound measure, CVP was part of the fluid-intolerance signal panel and is described here for completeness. CVP was measured through a central venous catheter connected to a pressure transducer leveled and zeroed at the phlebostatic axis, and the value was read at end-expiration. The change from baseline after a bolus (ΔCVP) was recorded to capture dynamic worsening.

Prespecified risk categories: low risk, < 12 mmHg; intermediate risk, 12–15 mmHg or a rise of 3 mmHg after a fluid bolus; high risk, > 15 mmHg or a rise of > 5 mmHg [6,7].

5. Risk-threshold summary

Thresholds were defined a priori and are summarized below (Additional file Fig. 2).



Variable for risk stratification	Green	Yellow	Red
Anterolateral LUS	Baseline <10	10-14 or an increase of 2 points from baseline	>14 or an increase >4 points from baseline
VExUS	0-1	2	3
E/lateral e'	<8	8-13	>13
CVP	Baseline <12 mmHg	12-15 or an increase of 3 mmHg from baseline	>15 or an increase >5 mmHg from baseline

Additional file Fig. 2. Fluid-intolerance signals and traffic-light risk stratification.

6. Overall traffic-light classification

For each assessment, the overall traffic-light category was determined by the worst (highest-risk) signal across the four domains: any red signal classified the patient as red; in the absence of a red signal, any yellow signal classified the patient as yellow; otherwise the patient was classified as green. The category set the bolus decision: 500 mL for green, 250 mL for yellow, and no further bolus for red, with early transition to alternative resuscitation strategies when fluids were withheld. When a signal could not be obtained, classification was based on the remaining available signals.

References

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