**Supplementary Digital Content**

# The Impact of Clinical Recognition of Acute Respiratory Distress Syndrome on Evidenced-Based Interventions in the Medical Intensive Care Unit

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**Supplementary Methods**

*Classification performance of clinician-recognized ARDS: stratified analyses*. We compared four statistical measures of classification performance (sensitivity [Se] specificity [Sp], positive predictive value [PPV], and negative predictive values [NPV]) of clinician-recognized ARDS (CR-ARDS) in two stratified analyses. The first stratified patients based on severity of oxygenation impairment using $PaO_2$:$FiO_2$ ratio where mild = $PaO_2$:$FiO_2$ ≥ 201, moderate = $PaO_2$:$FiO_2$ between 101 – 200, and severe = $PaO_2$:$FiO_2$ ≤ 201. The second stratified analysis was based on whether patients were enrolled prior to publication of the Berlin ARDS definition (while the American-European Consensus Conference [AECC] definition was still in use) versus after publication of the Berlin definition (June 20, 2012) (1, 2). Using the diagnostic era stratified analysis as an example, for each statistical measure of classification performance, we state the null hypothesis as there is no difference in the measure among ARDS patients admitted before June 20, 2012 versus ARDS patients admitted after that date. For sensitivity, the null hypothesis is:

$$H_0: Se_{\text{AECC}} = Se_{\text{Berlin}} \quad \text{(Eq. 1)}$$

As each statistical measure can be expressed as a proportion (e.g. sensitivity = True Positives / [True Positives + False Negatives], specificity = True Negatives / [True Negatives + False Positives], etc.), then the null hypothesis can also be expressed as a test of two proportions:

$$H_0 : \frac{TP_{AECC}}{TP_{AECC}+FN_{AECC}} = \frac{TP_{Berlin}}{TP_{Berlin}+FN_{Berlin}} \quad \text{(Eq. 2)}$$

As we are testing independent strata of patients, any test of binomial proportions is appropriate. Therefore, we can constructs a contingency table for each statistical measure and apply Pearson's $\chi^2$ test to assess if there is a difference between groups. Again using sensitivity as an example:

| *Sensitivity* | True Positive | False Negative |
|---|---|---|
| $\text{CR-ARDS}_{\text{AECC}}$ | $\text{TP}_{\text{AECC}}$ | $\text{FN}_{\text{AECC}}$ |
| $\text{CR-ARDS}_{\text{Berlin}}$ | $\text{TP}_{\text{Berlin}}$ | $\text{FN}_{\text{Berlin}}$ |

Results of these stratified analyses among patients based on severity of oxygenation impairment are shown in **Supplementary Table 3** and those stratified by enrollment before or after publication of the Berlin ARDS definition are shown in **Supplementary Table 4**.

*Cumulative net fluid balance during study period*. In all analyses of cumulative net fluid balance, we excluded patients who received continuous bladder irrigation while in the ICU ($n$ = 3) as urine output measurements for these patients were unreliable. We also excluded patients who received acute renal replacement therapy (RRT) while in the ICU ($n$ = 77), leaving 301 patients for the analyses (**Figure 1**). Acute RRT patients were excluded because (a) this patient population was specifically excluded from the fluid management arm of the Fluids and Catheter Treatment Trial (3); (b) fluid management while receiving dialysis is no longer under sole control of the ICU clinician, as dialysis ultra-filtrate volumes are set by the prescribing nephrologist; and (c) ICU clinicians' primary modality to manage volume overload (administering diuretics) is generally ineffective both while patients receive dialysis as well as during the oliguric / anuric period leading up to initiation of dialysis. Cumulative net fluid balance was compared among CR-ARDS and UR-ARDS patients for each study day using the Mann-Whitney *U* test. For each study day, patients who had died, discharged, or were transferred out of the ICU were excluded from the analysis and for all subsequent study days.

*Multivariable linear mixed-effects regression model for cumulative net fluid balance*. We tested the association between CR-ARDS and cumulative fluid balance using a multivariable linear mixed-effects regression model to account for the inherent temporal correlation across multiple daily observations for each patient. The regression model used an identity link function and a random intercept for each patient. In an unadjusted analysis, the fixed effects included study day (ICU Day 1 through 7) and clinician-recognition of ARDS (vs UR-ARDS). In an adjusted analysis, we selected confounders to include in the model using a directed acyclic graph to identify the clinical features

thought to influence both the exposure of interest (recognition of ARDS by ICU clinicians) as well as the outcome (net fluid balance) (**Supplementary Figure 2**). The fixed effects included in the final adjusted model are described in **Supplementary Table 2**. The regression analyses were performed in R (version 3.3.0) using the package *lmerTest* to estimate parameters of the linear mixed-effects models as well as to obtain confidence intervals and *p*-values (4).

**Supplementary References**


1. Bernard GR, Artigas A, Brigham KL, et al.: The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994; 149:818–824

2. The ARDS Definition Task Force: Acute Respiratory Distress Syndrome: The Berlin Definition. *JAMA* 2012; 307:2526–2533

3. The Acute Respiratory Distress Syndrome Network: Comparison of Two Fluid-Management Strategies in Acute Lung Injury. *New England Journal of Medicine* 2006; 354:2564–2575

4. Kuznetsova A, Brockhoff PB, Christensen RHB: lmerTest Package: Tests in Linear Mixed Effects Models. *Journal of Statistical Software* 2017; 82:1–26

**Supplementary Table 1. Intravenous Furosemide Equivalence Table for Loop Diuretics**

| Drug | Route | Intravenous Furosemide Equivalents (mg furosemide / mg drug) |
|---|---|---|
| Furosemide | Oral | 0.5 |
| Torsemide | Oral | 2 |
| Bumetanide | Intravenous | 40 |
| | Oral | 40 |

**Supplementary Table 2. Definitions and categorizations of variables in multivariable mixed-effects regression model**

| Variable | Description | Treatment of variables in regression analysis |
|---|---|---|
| Day | Study observation day | Ordinal value from 1 to 7 |
| Hemodynamic instability | Presence of shock on admission | Yes/no |
| Oxygenation impairment | Lowest $PaO_2$:$FiO_2$ and/or $SpO_2$:$FiO_2$ ratio during the first four ICU days | Ordinal categories:<br><br>3: Severe ARDS<br>• $PaO_2$:$FiO_2$ ≤ 100<br><br>2: Moderate ARDS<br>• $PaO_2$:$FiO_2$ ≥ 101 and ≤ 200<br><br>1: Mild ARDS<br>• $PaO_2$:$FiO_2$ ≥ 201 and ≤ 300<br><br>0: ARDS met by $SpO_2$:$FiO_2$ criteria alone<br>• Lowest $PaO_2$:$FiO_2$ > 300<br>• Lowest $SpO_2$:$FiO_2$ ≤ 315 *while* SpO2 > 96% |
| Medical history | Presence of diagnosis of congestive heart failure or chronic kidney disease in patient's medical history | Yes/no |
| Clinician-recognized ARDS | Documentation that a treating clinician either suspected or confirmed a diagnosis of ARDS | Yes/no |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

**Supplementary Table 3. Patient characteristics of entire study population**

| | Without ARDS | ARDS | *p*[f] |
|---|---|---|---|
| **Demographics** | **N = 596** | **N = 381** | |
| Age (years) | 56 [46 - 66] | 54 [41 - 65] | 0.04 |
| Gender (Female) | 271 (45.5) | 192 (50.4) | 0.13 |
| Race (Caucasian) | 499 (83.7) | 325 (85.3) | 0.51 |
| **Co-morbid Medical Disease** | | | |
| Pulmonary | 119 (25.5) | 73 (22.1) | 0.26 |
| Diabetes | 179 (30.0) | 112 (29.4) | 0.83 |
| Immunodeficiency | 161 (27.0) | 118 (31.0) | 0.18 |
| Congestive heart failure | 79 (13.3) | 42 (11.0) | 0.30 |
| Chronic kidney disease | 119 (20.0) | 72 (18.9) | 0.68 |
| Maintenance hemodialysis | 37 (6.2) | 16 (4.2) | 0.18 |
| Chronic liver disease | 75 (12.6) | 54 (14.2) | 0.47 |
| Solid tumor malignancy | 63 (13.5) | 47 (14.2) | 0.78 |
| Hematological malignancy | 49 (10.5) | 46 (13.9) | 0.15 |
| **ICU Admission Characteristics**[a] | | | |
| Source of admission[b] | | | <0.001[g] |
| Emergency department | 236 (40.5) | 122 (32.4) | |
| Hospital ward | 138 (23.7) | 136 (36.2) | |
| Transfer from another hospital | 188 (32.2) | 109 (29.0) | |
| Operating room | 11 (1.9) | 7 (1.9) | |
| Other | 10 (1.7) | 2 (0.5) | |
| ARDS risk factor[c] | | | <0.001[g] |
| Extrapulmonary Sepsis | 184 (33.0) | 128 (33.7) | |
| Pneumonia | 100 (17.9) | 126 (33.2) | |
| Aspiration | 63 (11.3) | 91 (23.9) | |
| Multiple transfusions | 39 (7.0) | 9 (2.4) | |
| Other[d] | 62 (28.9) | 24 (6.3) | |
| None | 110 (19.7) | 2 (0.5) | |
| Severe sepsis | 319 (53.5) | 313 (82.2) | <0.001 |
| Shock | 374 (62.8) | 264 (69.3) | 0.04 |
| Renal replacement therapy in ICU | 94 (15.8) | 77 (20.2) | 0.08 |
| APACHE II score | 28 [22 - 34] | 30 [24 - 36] | <0.001 |
| **Respiratory Characteristics**[a] | | | |
| Respiratory rate (breaths/min) | 28 [23 – 33] | 31 [26 - 37] | < 0.001 |
| Lowest $PaO_2/FiO_2$[e] | 195 [124 - 300] | 122 [78 - 184] | < 0.001 |

[a] Values for day of study enrollment (ICU Day 1).
[b] Source of admission available for 959 patients (583 without ARDS, 376 with ARDS).
[c] ARDS risk factor available for 938 patients (558 without ARDS, 380 with ARDS).
[d] "Other" category includes pancreatitis (13 without ARDS, 2 with ARDS), severe trauma (5 without ARDS, 2 with ARDS), drug overdose (40 without ARDS, 3 with ARDS), and other rare risk factors (3 without ARDS, 17 with ARDS) including tumor lysis syndrome, sickle cell crisis, pulmonary graft-versus-host disease, eosinophilic pneumonia, alveolar hemorrhage, and acute pulmonary drug toxicity.

[e] $PaO_2/FiO_2$ ratio available in 632 patients (366 without ARDS, 266 with ARDS).
[f] Statistical testing performed using Pearson's $\chi^2$ test for categorical variables unless otherwise noted, and Mann-Whitney U test for ordinal and continuous variables.
[g] Statistical testing by two-tailed Fisher's exact test.

**Supplementary Table 4. Contingency tables for comparison of classification metrics stratified by oxygenation severity**

| Statistical Measure | Oxygenation Impairment | Correctly Classified (Frequency) | Comparator (Frequency) | Measure Value (by group) | *p* |
|---|---|---|---|---|---|
| Sensitivity | | True Positive | False Negative | | < 0.001 |
| | Mild | 17 | 38 | 0.31 | |
| | Moderate | 51 | 61 | 0.46 | |
| | Severe | 70 | 30 | 0.70 | |
| Positive Predictive Value | | True Positive | False Positive | | 0.16 |
| | Mild | 17 | 7 | 0.71 | |
| | Moderate | 51 | 17 | 0.75 | |
| | Severe | 70 | 12 | 0.85 | |
| Specificity | | True Negative | False Positive | | < 0.001 |
| | Mild | 171 | 7 | 0.96 | |
| | Moderate | 108 | 17 | 0.86 | |
| | Severe | 53 | 12 | 0.82 | |
| Negative Predictive Value | | True Negative | False Negative | | < 0.001 |
| | Mild | 171 | 38 | 0.82 | |
| | Moderate | 108 | 61 | 0.64 | |
| | Severe | 53 | 30 | 0.64 | |

Abbreviations: ARDS, acute respiratory distress syndrome. Oxygenation severity groups: mild = $PaO_2$:$FiO_2$ ≥ 201, moderate = $PaO_2$:$FiO_2$ 101 – 200, severe = $PaO_2$:$FiO_2$ ≤ 100. Statistical tests were performed using Pearson's $\chi^2$-test.

**Supplementary Table 5. Contingency tables for comparison of classification metrics stratified by ARDS diagnostic era.**

| Statistical Measure | ARDS Diagnostic Era | Correctly Classified (Frequency) | Comparator (Frequency) | Measure Value (by Era) | *p* |
|---|---|---|---|---|---|
| Sensitivity | | True Positive | False Negative | | 0.21 |
| | AECC | 148 | 153 | 0.49 | |
| | Berlin | 33 | 47 | 0.41 | |
| Positive Predictive Value | | True Positive | False Positive | | < 0.001 |
| | AECC | 148 | 31 | 0.83 | |
| | Berlin | 33 | 22 | 0.60 | |
| Specificity | | True Negative | False Positive | | 0.07 |
| | AECC | 382 | 31 | 0.93 | |
| | Berlin | 161 | 22 | 0.88 | |
| Negative Predictive Value | | True Negative | False Negative | | 0.10 |
| | AECC | 382 | 153 | 0.71 | |
| | Berlin | 161 | 47 | 0.77 | |

Abbreviations: ARDS, acute respiratory distress syndrome; AECC, American-European Consensus Conference.

AECC indicates patients admitted prior to June 20, 2012 (date of publication of the Berlin ARDS definition), Berlin indicates patients admitted after June 20, 2012 (2). Statistical tests were performed using Pearson's $\chi^2$-test.

**Supplementary Table 6. Onset of Expert-Adjudicated ARDS in Study Population**

| Study Day | Clinician-Recognized ARDS | Unrecognized ARDS |
|---|---|---|
| ICU Day 1 | 143 (79.0) | 159 (79.5) |
| ICU Day 2 | 25 (13.8) | 24 (12.0) |
| ICU Day 3 | 6 (3.3) | 8 (4.0) |
| ICU Day 4 | 7 (3.9) | 9 (4.5) |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Date of first presence of ARDS by expert adjudication in the study population. $p = 0.93$ by Pearson's $\chi^2$-test between clinician-recognized ARDS and unrecognized ARDS patients.

**Supplementary Table 7. Ventilator Set Tidal Volumes by Study Day**

| Study Day | No. Patients[a] | Clinician-Recognized ARDS | Unrecognized ARDS | *p* |
|---|---|---|---|---|
| ICU Day 1 | 240 | 6.60 (±1.10) | 6.40 (±0.90) | 0.49 |
| ICU Day 2 | 328 | 6.59 (±1.02) | 6.47 (±0.90) | 0.4 |
| ICU Day 3 | 278 | 6.52 (±1.06) | 6.51 (±0.88) | 0.87 |
| ICU Day 4 | 234 | 6.50 (±1.11) | 6.47 (±0.92) | 0.93 |
| ICU Day 5 | 191 | 6.57 (±1.08) | 6.53 (±0.93) | 0.83 |
| ICU Day 6 | 154 | 6.50 (±0.95) | 6.53 (±0.93) | 0.98 |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Set tidal volumes presented as volume normalized to predicted body weight, in milliliters per kilogram. Values are presented as mean (±sample standard deviation). Statistical tests between groups were performed using the Mann-Whitney *U* Test.

[a] Number of patients with available data.

**Supplementary Table 8. Ventilator Set Positive End Expiratory Pressure by Study Day**

| Study Day | No. Patients[a] | Clinician-Recognized ARDS | Unrecognized ARDS | *p* |
|---|---|---|---|---|
| ICU Day 1 | 243 | 9.7 (±3.4) | 7.7 (±2.8) | <0.001 |
| ICU Day 2 | 336 | 9.0 (±3.4) | 7.1 (±2.5) | <0.001 |
| ICU Day 3 | 288 | 8.8 (±3.2) | 6.7 (±2.5) | < 0.001 |
| ICU Day 4 | 246 | 8.6 (±3.4) | 6.9 (±2.7) | < 0.001 |
| ICU Day 5 | 203 | 8.1 (±3.1) | 7.1 (±2.8) | 0.006 |
| ICU Day 6 | 161 | 8.0 (±3.1) | 6.8 (±2.6) | 0.011 |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

Set positive end expiratory pressure in centimeters of water (cm $H_2O$). Values are presented as mean (±sample standard deviation). Statistical tests between groups were performed using the Mann-Whitney *U* Test.

[a] Number of patients with available data.

**Supplementary Table 9. Cumulative Net Fluid Balance by Study Day**

| Cumulative Period | Clinician-Recognized ARDS | Unrecognized ARDS | Groupwise Mean Difference | *p* |
|---|---|---|---|---|
| ICU Day 1 | 1481 [-21; 3091] (144) | 1205 [148; 3472] (156) | 51 (-642, +743) | 1.00 |
| Through ICU Day 2 | 2367 [98; 5687] (144) | 3004 [408; 5005] (156) | -70 (-1112, +973) | 0.53 |
| Through ICU Day 3 | 2985 [132; 6863] (139) | 4089 [1063; 7501] (152) | -836 (-1983, +310) | 0.15 |
| Through ICU Day 4 | 3326 [-127; 7730] (134) | 4301 [967; 8023] (138) | -862 (-2131, +408) | 0.28 |
| Through ICU Day 5 | 3529 [-423; 7056] (125) | 4452 [881; 8034] (130) | -1066 (-2475, +343) | 0.15 |
| Through ICU Day 6 | 2891 [-554; 6605] (117) | 4489 [175; 8908] (116) | -1415 (-2980, +150) | 0.086 |
| Through ICU Day 7 | 3184 [-1000; 6378] (106) | 4634 [168; 8781] (110) | -1737 (-3403, -69) | 0.039 |

Abbreviations: ARDS, acute respiratory distress syndrome. Group values are presented as median [Interquartile range] (Number of patients with observations). Groupwise difference is presented as Difference in Means (95% confidence interval). Statistical tests between groups were performed using the Mann-Whitney *U* Test.

**Supplementary Table 10. Cumulative Diuretic Administration by Study Day**

| | Clinician-Recognized ARDS | | Unrecognized ARDS | | |
|---|---|---|---|---|---|
| **Study Day** | **Dose Administered (mg / 24 hrs)** | **Received ≥1 Dose No. (%)** | **Dose Administered (mg / 24 hrs)** | **Received ≥1 Dose No. (%)** | ***p*** |
| ICU Day 1 | 14 [0; 0] | 25 (17.4) | 21 [0; 0] | 26 (16.6) | 0.91 |
| Through ICU Day 2 | 34 [0; 40] | 45 (31.2) | 42 [0; 0] | 31 (19.7) | 0.06 |
| Through ICU Day 3 | 55 [0; 45] | 55 (38.2) | 66 [0; 20] | 45 (28.7) | 0.12 |
| Through ICU Day 4 | 74 [0; 80] | 61 (42.4) | 97 [0; 60] | 48 (30.5) | 0.26 |
| Through ICU Day 5 | 96 [0; 120] | 68 (47.2) | 124 [0; 80] | 55 (35.0) | 0.08 |
| Through ICU Day 6 | 116 [0; 160] | 70 (48.6) | 138 [0; 80] | 55 (35.0) | 0.03 |
| Through ICU Day 7 | 134 [0; 200] | 71 (49.3) | 157 [0; 80] | 56 (35.7) | 0.02 |

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

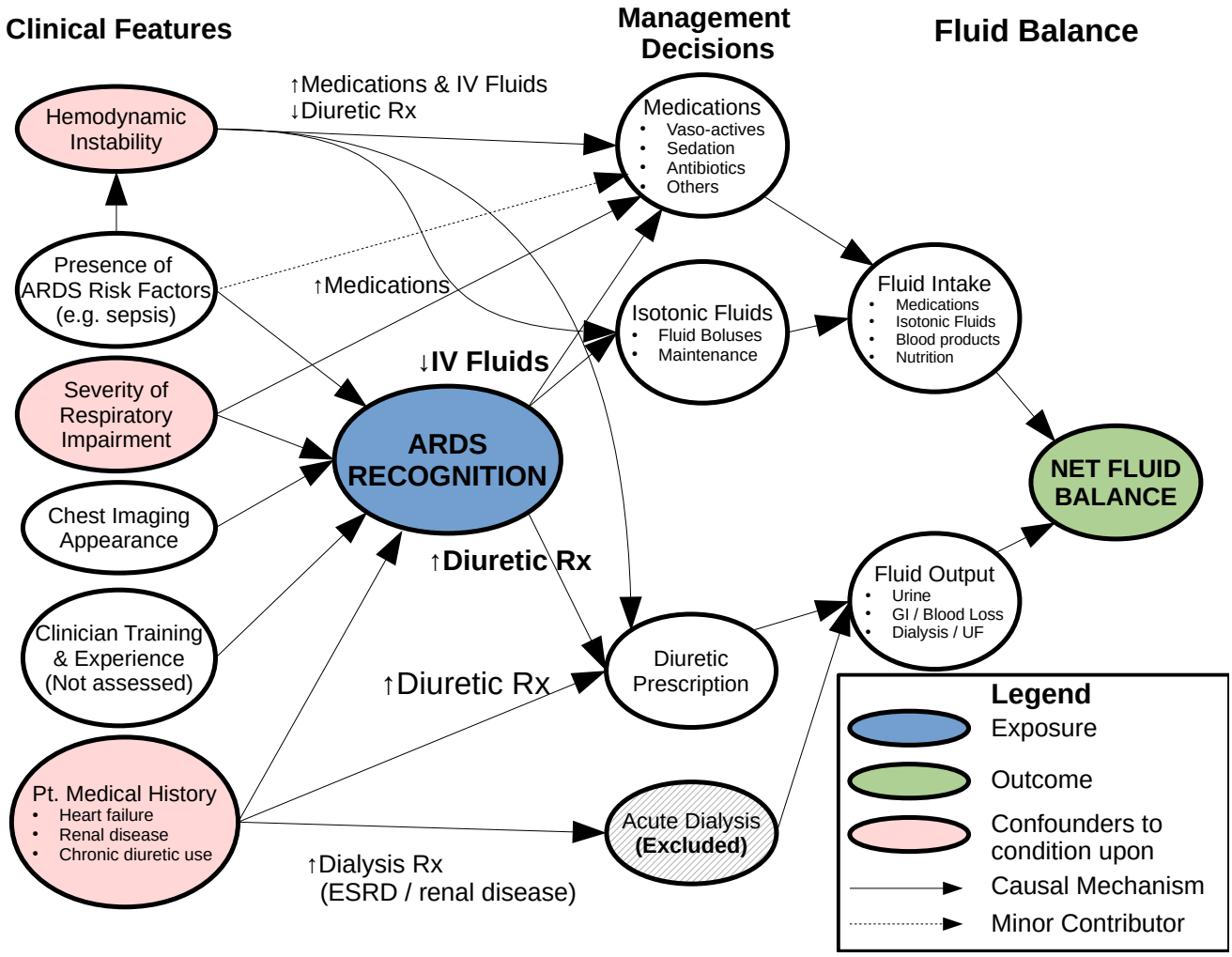
Cumulative diuretics administered in milligrams of intravenous furosemide equivalents over the observation period, and number of subjects who received at least 1 diuretic dose, by day among patients who did not receive acute hemodialysis. Cumulative dose administered are presented as mean [25%; 75% percentile]. Mean is reported as the measure of central tendency because <50% of patients in both groups ever received a diuretic during the study observation period, therefore daily medians are zero for all daily comparisons. Note that 75% percentile is higher among clinician-recognized ARDS versus unrecognized ARDS for ICU days 2 through 7. Statistical tests between groups were performed using the Mann-Whitney *U* Test on cumulative dose of administered diuretics.

**Supplementary Table 11. Lowest Central Venous Pressure by Study Day**

| Study Day | No. Patients[a] | Clinician-Recognized ARDS | Unrecognized ARDS | *p* |
|---|---|---|---|---|
| ICU Day 1 | 120 | 11.9 (±5.1) | 11.9 (±5.7) | 0.58 |
| ICU Day 2 | 206 | 11.4 (±4.8) | 11.4 (5.4) | 0.87 |
| ICU Day 3 | 192 | 11.1 (±4.8) | 12.1 (±6.8) | 0.20 |
| ICU Day 4 | 171 | 12.2 (±6.6) | 11.7 (±5.9) | 0.67 |
| ICU Day 5 | 139 | 10.9 (±7.1) | 11.0 (±6.6) | 0.43 |
| ICU Day 6 | 125 | 9.7 (±5.7) | 11.6 (±8.0) | 0.11 |

Central venous pressure in centimeters of water (cm $H_2O$). Values are presented as mean (±sample standard deviation). Statistical tests between groups were performed using the Mann-Whitney *U* Test.
[a] Number of patients with available data.

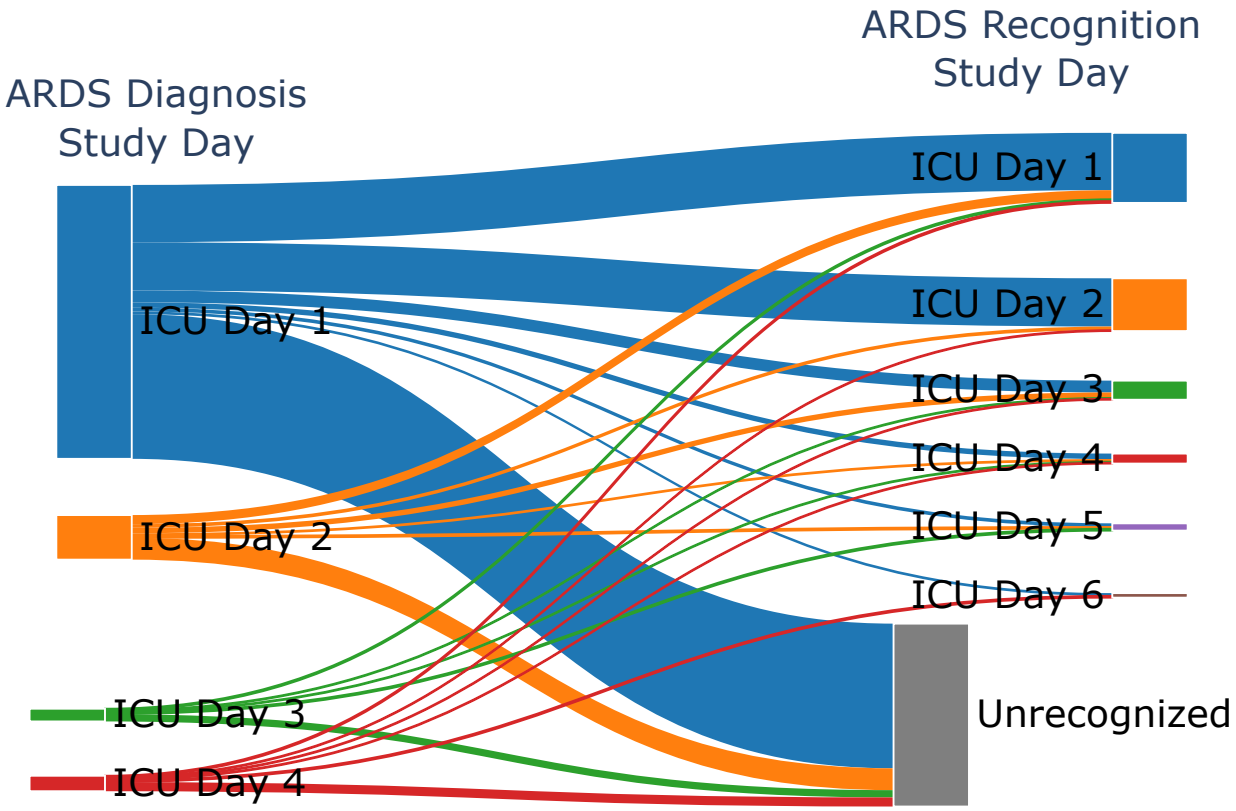
**Supplementary Figures**




**Supplementary Figure 1. Directed acyclic graph for confounder selection in multivariable regression model of cumulative net fluid balance.** Nodes on the left column indicate Clinical Features thought to influence ARDS recognition (blue node, exposure of interest). Nodes to the right of "ARDS Recognition" indicate Management Decisions that ultimately influence net fluid balance (green node, outcome of interest). Arrows indicate potential causal effects linking the clinical features to management decisions. Labels on select arrows indicate the specific causal effect (e.g. presence of hemodynamic instability may lead clinicians to prescribe more medications and intravenous fluids, whereas the presence of underlying heart failure or chronic kidney disease may lead clinicians to prescribe more diuretics). Nodes in red indicate confounders which were included in the multivariable mixed-effects regression model to close open "back-door" paths from ARDS Recognition to Net Fluid Balance. Some clinical features that influence ARDS Recognition were not conditioned upon in the multivariable regression model (Notably, "Chest Imaging Appearance" and "Clinician Training & Experience") as they were thought to only influence the outcome directly through ARDS Recognition, and did not have an independent causal link to the outcome.

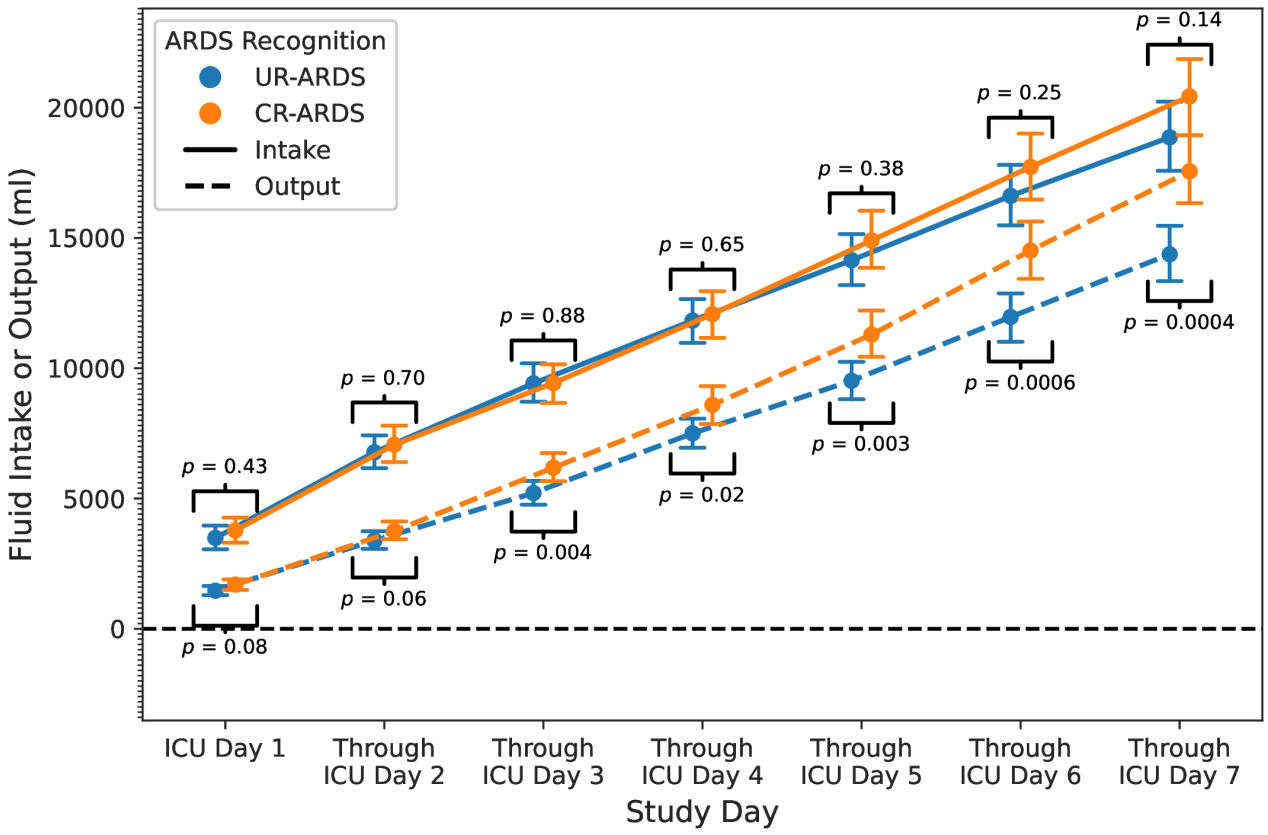
Note that although “ARDS Risk Factor” is left as a potentially open “back-door” path (dotted arrow), we did not condition upon this clinical feature in the regression model because the effect of ARDS Risk Factor on net fluid balance was minimal compared to the downstream clinical feature “Hemodynamic Instability”. Conceptually, although common ARDS risk factors in the medical ICU such as sepsis or pneumonia may lead to increased prescription of intravenous medications (particularly antibiotics), this effect of net fluid is substantially overwhelmed by that of hemodynamic instability, which is also associated with increased prescription of intravenous antibiotics, vasoactive agents, and other medications.

As noted in the **Supplementary Methods**: patients who received acute dialysis (hatched node) while in the ICU ($n$ = 77) were excluded from the cumulative fluid analyses because: this patient population was excluded from the fluid management arm of the Fluids and Catheter Treatment Trial (3); fluid management while receiving dialysis is no longer under sole control of the ICU clinician, as dialysis ultra-filtrate volumes are set by the prescribing nephrologist; and clinicians were unlikely to be successful at using diuretics to control volume overload both while patients were receiving dialysis as well as during the oliguric / anuric period leading up to initiation of dialysis.




**Supplementary Figure 2. Timing of ARDS onset and clinical ARDS recognition**. Alluvial plot demonstrating timing of ARDS onset by expert adjudication (left side) and clinician recognition of ARDS as documented in the electronic medical record (right side) among the 381 patients with ARDS.

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit.




**Supplementary Figure 3. Cumulative fluid intake and output by study day.**

Cumulative fluid intake (solid lines) and output (dashed lines) over the first 7 ICU days. Dots represent group means by day, error bars represent 95% confidence intervals for the group means. Statistical comparisons between groups were performed using the Mann-Whitney *U* Test, with upper brackets illustrating statistical tests for fluid intake and lower brackets illustrating statistical tests for fluid output. Abbreviations: ARDS, acute respiratory distress syndrome; CR-ARDS, clinician-recognized ARDS; UR-ARDS, unrecognized ARDS.