**Table 1. Baseline Characteristics of the Derivation and Validation Cohorts**

| Variable | Ruijin derivation cohort (n=150) | Fujian retrospective validation cohort (n=505) | Fuyang prospective validation cohort (n=340) | Overall (n=995) |
|---|---|---|---|---|
| Age, years | 63 [52–72] | 61 [50–71] | 62 [51–70] | 62 [51–71] |
| Male sex, n (%) | 96 (64.0) | 325 (64.4) | 219 (64.4) | 640 (64.3) |
| BMI, kg/m² | 24.1 [22.0–26.8] | 23.8 [21.7–26.1] | 24.0 [22.1–26.4] | 23.9 [21.9–26.3] |
| APACHE II score | 22 [18–28] | 21 [17–27] | 23 [18–29] | 22 [18–28] |
| SOFA score at enrollment | 10 [8–13] | 9 [7–12] | 10 [8–13] | 10 [7–12] |
| Lactate, mmol/L | 2.1 [1.4–3.3] | 1.9 [1.3–3.0] | 2.2 [1.5–3.4] | 2.0 [1.4–3.2] |
| $PaO_2/FiO_2$ ratio at baseline, mmHg | 176 [118–228] | 185 [126–240] | 171 [112–223] | 179 [120–232] |
| pH | 7.37 [7.31–7.42] | 7.38 [7.32–7.43] | 7.36 [7.30–7.42] | 7.37 [7.31–7.43] |
| $PaCO_2$, mmHg | 41 [35–49] | 40 [34–47] | 42 [35–50] | 41 [35–48] |
| PEEP, $cmH_2O$ | 10 [8–12] | 10 [8–12] | 10 [8–12] | 10 [8–12] |
| $FiO_2$ | 0.60 [0.50–0.80] | 0.60 [0.45–0.75] | 0.60 [0.50–0.80] | 0.60 [0.50–0.80] |
| Invasive mechanical ventilation at enrollment, n (%) | 132 (88.0) | 426 (84.4) | 298 (87.6) | 856 (86.0) |

| | | | | |
|---|---|---|---|---|
| Vasopressor use, n (%) | 68 (45.3) | 201 (39.8) | 151 (44.4) | 420 (42.2) |
| Renal replacement therapy, n (%) | 19 (12.7) | 52 (10.3) | 41 (12.1) | 112 (11.3) |
| Direct ARDS, n (%) | 91 (60.7) | 319 (63.2) | 205 (60.3) | 615 (61.8) |
| Pneumonia, n (%) | 83 (55.3) | 278 (55.0) | 186 (54.7) | 547 (55.0) |
| Sepsis, n (%) | 71 (47.3) | 226 (44.8) | 160 (47.1) | 457 (45.9) |
| Chronic pulmonary disease, n (%) | 21 (14.0) | 67 (13.3) | 45 (13.2) | 133 (13.4) |
| Chronic cardiovascular disease, n (%) | 39 (26.0) | 120 (23.8) | 82 (24.1) | 241 (24.2) |
| Diabetes mellitus, n (%) | 28 (18.7) | 101 (20.0) | 66 (19.4) | 195 (19.6) |
| Immunocompromised status, n (%) | 16 (10.7) | 47 (9.3) | 33 (9.7) | 96 (9.6) |
| Baseline higher-inflammatory phenotype, n (%) | 63 (42.0) | 210 (41.6) | 144 (42.4) | 417 (41.9) |
| Baseline lower-inflammatory phenotype, n (%) | 87 (58.0) | 295 (58.4) | 196 (57.6) | 578 (58.1) |

**Abbreviations:** ARDS, acute respiratory distress syndrome; BMI, body mass index; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; PEEP, positive end-expiratory pressure.

**Table 2. Early oxygenation, organ dysfunction, and support intensity across trajectory classes in the derivation cohort**

| Variable | Rapid improvers (n=54) | Intermediate resolvers (n=53) | Refractory trajectory (n=43) | P value |
|---|---|---|---|---|
| **Day 1** | | | | |
| $PaO_2/FiO_2$ ratio, mmHg | 238.4 ± 54.1 | 186.3 ± 41.8 | 103.1 ± 28.5 | <0.001 |
| SOFA score | 8 [6–10] | 10 [8–12] | 12 [10–14] | <0.001 |
| $FiO_2$ | 0.50 [0.45–0.60] | 0.60 [0.50–0.70] | 0.80 [0.70–0.90] | <0.001 |
| PEEP, $cmH_2O$ | 8 [8–10] | 10 [8–12] | 12 [10–14] | <0.001 |
| Vasopressor use, n (%) | 16 (29.6) | 24 (45.3) | 28 (65.1) | 0.002 |
| RRT, n (%) | 4 (7.4) | 6 (11.3) | 9 (20.9) | 0.12 |

| | | | | |
|---|---|---|---|---|
| **Day 2** | | | | |
| $PaO_2/FiO_2$ ratio, mmHg | 284.7 ± 62.0 | 190.1 ± 44.5 | 94.8 ± 26.7 | <0.001 |
| SOFA score | 7 [5–9] | 10 [8–12] | 12 [10–15] | <0.001 |
| $FiO_2$ | 0.45 [0.40–0.55] | 0.55 [0.50–0.70] | 0.80 [0.70–0.90] | <0.001 |
| PEEP, $cmH_2O$ | 8 [6–10] | 10 [8–12] | 12 [10–14] | <0.001 |
| Vasopressor use, n (%) | 12 (22.2) | 21 (39.6) | 27 (62.8) | <0.001 |
| RRT, n (%) | 4 (7.4) | 7 (13.2) | 10 (23.3) | 0.08 |
| **Day 3** | | | | |

| | | | | |
|---|---|---|---|---|
| $PaO_2/FiO_2$ ratio, mmHg | 320.4 ± 70.3 | 192.1 ± 49.7 | 87.0 ± 24.1 | <0.001 |
| SOFA score | 6 [4–8] | 9 [7–11] | 13 [10–15] | <0.001 |
| $FiO_2$ | 0.40 [0.35–0.50] | 0.55 [0.45–0.65] | 0.85 [0.70–1.00] | <0.001 |
| PEEP, $cmH_2O$ | 8 [6–10] | 10 [8–12] | 12 [10–14] | <0.001 |
| Vasopressor use, n (%) | 9 (16.7) | 19 (35.8) | 26 (60.5) | <0.001 |
| RRT, n (%) | 3 (5.6) | 7 (13.2) | 11 (25.6) | 0.02 |

**Abbreviations:** RRT, renal replacement therapy.

**Table 3. Multinomial logistic regression for the association between baseline inflammatory phenotype and early clinical trajectory**

Reference trajectory class: **Intermediate resolvers**

| Predictor | Rapid improvers vs intermediate resolvers, adjusted OR (95% CI) | P value | Refractory vs intermediate resolvers, adjusted OR (95% CI) | P value |
|---|---|---|---|---|
| **Higher-inflammatory phenotype** | 0.54 (0.29–0.98) | 0.043 | 2.81 (1.59–4.95) | <0.001 |
| **Lower-inflammatory phenotype** | 1.00 (reference) | — | 1.00 (reference) | — |
| **Age, per 10-year increase** | 0.91 (0.73–1.14) | 0.41 | 1.12 (0.90–1.39) | 0.31 |
| **Male sex** | 1.08 (0.56–2.06) | 0.82 | 1.14 (0.59–2.22) | 0.69 |
| **APACHE II, per 5-point increase** | 0.88 (0.68–1.14) | 0.34 | 1.36 (1.05–1.76) | 0.019 |
| **Baseline $PaO_2/FiO_2$, per 50-mmHg increase** | 1.29 (1.02–1.63) | 0.031 | 0.66 (0.50–0.87) | 0.004 |
| **Direct ARDS** | 1.18 (0.61–2.29) | 0.62 | 1.27 (0.67–2.42) | 0.47 |
| **Vasopressor use at baseline** | 0.73 (0.37–1.44) | 0.37 | 1.74 (0.89–3.42) | 0.11 |

**Interpretation note:** Compared with the lower-inflammatory phenotype, the higher-inflammatory phenotype was associated with lower odds of a rapid improvement trajectory and higher odds of a refractory trajectory.

**Table 4. Phenotype transition patterns over 72 hours and corresponding changes in oxygenation and organ dysfunction**

| Transition group | n (%) | ΔPaO₂/FiO₂ from Day 1 to Day 3, mmHg | Daily change in PaO₂/FiO₂, mmHg/day | ΔSOFA from Day 1 to Day 3 | Daily change in SOFA, points/day | ICU mortality, n (%) |
|---|---|---|---|---|---|---|
| Persistent lower-inflammatory | 402 (40.4) | +78.4 ± 64.2 | +39.2 ± 32.1 | -2.1 ± 2.4 | -1.05 ± 1.20 | 48 (11.9) |
| Persistent higher-inflammatory | 286 (28.7) | -8.7 ± 58.6 | -4.4 ± 29.3 | +0.9 ± 2.8 | +0.45 ± 1.40 | 92 (32.2) |
| Higher-to-lower conversion | 131 (13.2) | +64.6 ± 61.5 | +32.3 ± 30.8 | -1.8 ± 2.3 | -0.90 ± 1.15 | 19 (14.5) |
| Lower-to-higher conversion | 176 (17.7) | -21.4 ± 54.9 | -10.7 ± 27.5 | +1.2 ± 2.6 | +0.60 ± 1.30 | 46 (26.1) |
| P for overall comparison | — | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

**Abbreviations:** ICU, intensive care unit.

**Table 5. Short-term clinical outcomes according to early trajectory class across cohorts**

**Derivation cohort (Ruijin)**

| Outcome | Rapid improvers (n=54) | Intermediate resolvers (n=53) | Refractory trajectory (n=43) | P value |
|---|---|---|---|---|
| ICU mortality, n (%) | 11 (20.4) | 17 (32.1) | 23 (53.5) | 0.002 |
| 28-day mortality, n (%) | 12 (22.2) | 18 (34.0) | 24 (55.8) | 0.001 |
| Ventilator-free days at day 28 | 16 [0–22] | 9 [0–18] | 0 [0–8] | <0.001 |
| Duration of mechanical ventilation, days | 8 [5–14] | 12 [7–19] | 17 [10–25] | <0.001 |
| ICU length of stay, days | 13 [8–21] | 19 [12–28] | 28 [17–39] | <0.001 |
| Hospital length of stay, days | 21 [14–31] | 28 [18–39] | 34 [22–48] | <0.001 |

**Retrospective validation cohort (Fujian)**

| Outcome | Rapid improvers | Intermediate resolvers | Refractory trajectory | P value |
|---|---|---|---|---|
| ICU mortality, n (%) | 12 (6.4) | 16 (9.7) | 39 (25.3) | <0.001 |
| 28-day mortality, n (%) | 14 (7.4) | 19 (11.5) | 44 (28.6) | <0.001 |
| Ventilator-free days at day 28 | 19 [12–24] | 15 [7–21] | 6 [0–15] | <0.001 |

| | | | | |
|---|---|---|---|---|
| Duration of mechanical ventilation, days | 6 [4–10] | 8 [5–13] | 13 [8–21] | <0.001 |
| ICU length of stay, days | 8 [5–13] | 10 [7–15] | 15 [10–24] | <0.001 |
| Hospital length of stay, days | 16 [11–23] | 18 [13–27] | 24 [16–35] | <0.001 |

## Prospective validation cohort (Fuyang)

| Outcome | Rapid improvers | Intermediate resolvers | Refractory trajectory | P value |
|---|---|---|---|---|
| ICU mortality, n (%) | 14 (20.0) | 48 (61.5) | 33 (68.8) | <0.001 |
| 28-day mortality, n (%) | 15 (21.4) | 34 (70.8) | 50 (64.1) | <0.001 |
| Ventilator-free days at day 28 | 14 [0–21] | 3 [0–10] | 2 [0–9] | <0.001 |
| Duration of mechanical ventilation, days | 10 [6–16] | 20 [12–30] | 18 [10–29] | <0.001 |
| ICU length of stay, days | 16 [10–25] | 26 [16–39] | 24 [15–37] | <0.001 |
| Hospital length of stay, days | 24 [16–34] | 35 [24–49] | 32 [21–47] | <0.001 |

**Table 6. Incremental prognostic performance of early trajectory beyond the conventional baseline phenotype model for 28-day mortality**

| Model | Predictors included | C-statistic (95% CI) | ΔC-statistic vs previous model | Calibration slope | Brier score | Likelihood ratio test P value |
|---|---|---|---|---|---|---|
| Model 1 | Baseline clinical severity variables only | 0.71 (0.67–0.75) | — | 0.96 | 0.182 | — |
| Model 2 | Model 1 + baseline inflammatory phenotype | 0.78 (0.74–0.82) | +0.07 | 0.98 | 0.161 | <0.001 |
| Model 3 | Model 2 + early 72-hour trajectory class | 0.84 (0.81–0.88) | +0.06 | 1.01 | 0.138 | <0.001 |

**Additional reclassification metrics**

| Comparison | Continuous NRI (95% CI) | IDI (95% CI) | P value |
|---|---|---|---|
| Model 2 vs Model 1 | 0.24 (0.12–0.35) | 0.041 (0.019–0.067) | <0.001 |

| | | | |
|---|---|---|---|
| Model 3 vs Model 2 | 0.29 (0.17–0.42) | 0.056 (0.028–0.084) | <0.001 |
| Model 3 vs Model 1 | 0.47 (0.31–0.60) | 0.103 (0.068–0.141) | <0.001 |

Abbreviations: NRI, net reclassification improvement; IDI, integrated discrimination improvement.

Model 1 included prespecified baseline clinical severity variables. Model 2 represented the conventional baseline phenotype model by adding baseline inflammatory phenotype to Model 1. Model 3 further added early 72-hour trajectory class to Model 2. The primary outcome for all model comparisons was 28-day mortality.

**Supplementary Tables**

**Supplementary Table S1. Missing data rates and harmonization procedures for key variables**

| Variable | Ruijin missing, n (%) | Fujian missing, n (%) | Fuyang missing, n (%) | Harmonization method |
|---|---|---|---|---|
| IL-6 | 6 (4.0) | 31 (6.1) | 18 (5.3) | Standardized assay units; log transformation |
| TNFR1 | 8 (5.3) | 35 (6.9) | 21 (6.2) | Batch-adjusted z score |
| Procalcitonin | 4 (2.7) | 20 (4.0) | 13 (3.8) | Winsorization at 1st/99th percentile |
| Lactate | 2 (1.3) | 9 (1.8) | 7 (2.1) | Median imputation if isolated missing |
| $PaO_2/FiO_2$ Day 1 | 0 (0.0) | 6 (1.2) | 3 (0.9) | No imputation if unavailable for trajectory derivation |
| $PaO_2/FiO_2$ Day 2 | 5 (3.3) | 28 (5.5) | 16 (4.7) | Multiple imputation in sensitivity analysis |
| $PaO_2/FiO_2$ Day 3 | 7 (4.7) | 33 (6.5) | 19 (5.6) | Multiple imputation in sensitivity analysis |
| SOFA Day 1 | 0 (0.0) | 4 (0.8) | 2 (0.6) | Direct extraction from EHR |
| SOFA Day 2 | 3 (2.0) | 17 (3.4) | 10 (2.9) | Component-wise reconstruction |
| SOFA Day 3 | 4 (2.7) | 20 (4.0) | 11 (3.2) | Component-wise reconstruction |

**Supplementary Table S2. Robustness of trajectory classification under alternative model specifications**

| Specification | No. of classes selected | Entropy | BIC | Minimum class size | Clinical interpretability |
|---|---|---|---|---|---|
| 2-class model | 2 | 0.78 | 4120 | 43.3% | Moderate |
| 3-class model | 3 | 0.84 | 3985 | 28.7% | High |
| 4-class model | 4 | 0.86 | 3981 | 8.0% | Limited due to class fragmentation |
| 3-class model with SOFA included | 3 | 0.82 | 4011 | 25.4% | High |
| 3-class model with PEEP and $FiO_2$ included | 3 | 0.83 | 4005 | 27.1% | High |
| Spline-based longitudinal clustering | 3 | — | — | 24.8% | Similar pattern retained |

**Supplementary Table S3. Association between inflammatory phenotype and refractory trajectory stratified by ARDS etiology**

| Subgroup | Adjusted OR for higher-inflammatory phenotype predicting refractory trajectory (95% CI) | P value | Interaction P value |
|---|---|---|---|
| Direct ARDS | 2.63 (1.51–4.58) | <0.001 | |
| Indirect ARDS | 2.94 (1.42–6.06) | 0.004 | 0.71 |

**Supplementary Table S4. Key biomarker concentrations according to baseline phenotype and early trajectory class**

| Biomarker | Lower-inflammatory phenotype | Higher-inflammatory phenotype | Rapid improvers | Intermediate resolvers | Refractory trajectory |
|---|---|---|---|---|---|
| IL-6, pg/mL | 42 [18–96] | 186 [94–382] | 51 [22–110] | 98 [41–210] | 211 [102–430] |
| TNFR1, pg/mL | 1.8 [1.3–2.5] | 3.9 [2.8–5.5] | 2.0 [1.4–2.8] | 2.8 [1.9–4.1] | 4.2 [3.0–5.9] |
| Procalcitonin, ng/mL | 0.9 [0.3–2.6] | 4.1 [1.5–10.2] | 0.8 [0.3–2.0] | 1.9 [0.6–5.8] | 4.8 [1.7–12.4] |
| Lactate, mmol/L | 1.7 [1.2–2.5] | 2.8 [1.8–4.0] | 1.6 [1.1–2.2] | 2.0 [1.4–3.0] | 3.0 [2.0–4.4] |

**Supplementary Table S5. Secondary outcomes across trajectory classes**

| Outcome | Rapid improvers | Intermediate resolvers | Refractory trajectory | P value |
|---|---|---|---|---|
| Need for prone positioning, n (%) | 18 (14.0) | 55 (20.1) | 97 (37.5) | <0.001 |
| Need for neuromuscular blockade, n (%) | 25 (19.4) | 71 (25.9) | 109 (42.1) | <0.001 |
| Need for ECMO, n (%) | 2 (1.6) | 8 (2.9) | 18 (7.0) | 0.01 |
| Shock-free days at day 28 | 24 [18–27] | 19 [8–25] | 8 [0–21] | <0.001 |
| RRT-free days at day 28 | 28 [28–28] | 26 [20–28] | 18 [0–28] | <0.001 |

**Supplementary Table S6. Associations of continuous rates of change in oxygenation and SOFA with 28-day mortality**

| Continuous exposure | Adjusted OR for 28-day mortality (95% CI) | P value |
|---|---|---|
| Per 50-mmHg increase in $\Delta PaO_2/FiO_2$ from Day 1 to Day 3 | 0.72 (0.63–0.83) | <0.001 |
| Per 1-point decrease in ΔSOFA from Day 1 to Day 3 | 0.81 (0.74–0.89) | <0.001 |
| Faster oxygenation improvement tertile vs slowest tertile | 0.48 (0.32–0.71) | <0.001 |
| Worsening oxygenation vs stable oxygenation | 1.94 (1.33–2.82) | <0.001 |

**Supplementary Table S7. Sensitivity analyses for the association between trajectory class and mortality**

| Sensitivity analysis | Rapid improvers vs intermediate, adjusted OR (95% CI) for 28-day mortality | Refractory vs intermediate, adjusted OR (95% CI) for 28-day mortality | P value |
|---|---|---|---|
| Primary analysis | 0.58 (0.36–0.92) | 2.41 (1.58–3.67) | <0.001 |
| Complete-case analysis | 0.61 (0.37–1.00) | 2.33 (1.49–3.66) | <0.001 |
| After multiple imputation | 0.56 (0.35–0.88) | 2.48 (1.64–3.74) | <0.001 |
| Excluding transferred patients | 0.60 (0.37–0.97) | 2.29 (1.47–3.57) | <0.001 |
| Restricting to invasively ventilated patients | 0.54 (0.33–0.89) | 2.57 (1.66–3.98) | <0.001 |
| Restricting to Berlin moderate-to-severe ARDS | 0.52 (0.31–0.86) | 2.71 (1.73–4.24) | <0.001 |

Supplementary Table S8. Comparative prognostic performance of conventional baseline phenotype, early trajectory, and combined phenotype-plus-trajectory models for 28-day mortality

| Model | Predictors included | C-statistic (95% CI) | Calibration slope | Brier score | ΔC-statistic vs Model A | Continuous NRI vs Model A | IDI vs Model A |
|---|---|---|---|---|---|---|---|
| Model A | Baseline clinical severity variables + baseline inflammatory phenotype | 0.78 (0.74–0.82) | 0.98 | 0.161 | Reference | — | — |
| Model B | Baseline clinical severity variables + early 72-hour trajectory class | 0.81 (0.77–0.85) | 1.00 | 0.149 | +0.03 | 0.18 (0.07–0.30) | 0.027 (0.011–0.046) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Model C | Baseline clinical severity variables + baseline inflammatory phenotype + early 72-hour trajectory class | 0.84 (0.81–0.88) | 1.01 | 0.138 | +0.06 | 0.34 (0.20–0.47) | 0.064 (0.035–0.092) |

**Footnote:** Abbreviations: NRI, net reclassification improvement; IDI, integrated discrimination improvement. Model A represented the conventional baseline phenotype strategy. Model B evaluated early 72-hour trajectory as an alternative longitudinal stratification strategy. Model C evaluated the combined phenotype-plus-trajectory strategy. All models used 28-day mortality as the dependent variable. Baseline clinical severity variables were prespecified and identical across models. Comparative analyses were intended to assess complementary prognostic information rather than replacement of baseline phenotyping by trajectory alone.