1. Study Title

Association of the PaO□/PaCO□ Ratio With ICU Mortality Independent of Oxygen Saturation and Mean Arterial Pressure: A MIMIC-II Retrospective Cohort Study
Acronym: RATIO-MIMIC

2. Study Objectives

Primary Objective:

- To determine whether the PaO□/PaCO□ ratio is independently associated with ICU mortality in critically ill adults, adjusting for oxygen saturation (SpO□) and mean arterial pressure (MAP).

Secondary Objectives:

- To explore the relationship between PaO□/PaCO□ ratio categories (e.g., tertiles or quartiles) and ICU length of stay.
- To perform subgroup analyses by mechanical ventilation status, age, or primary ICU diagnosis.

3. Study Design

- **Type:** Observational
- **Design:** Retrospective cohort study
- **Population:** Adult ICU patients (≥18 years) in MIMIC-II database
- **Sampling Method:** Retrospective census of all eligible patients meeting inclusion/exclusion criteria
- **Cohorts/Groups:** Single cohort; exposure analyzed as continuous and categorical (quartiles or tertiles)
- **Time Frame:** ICU admissions from 2001–2008 (MIMIC-II database)

4. Study Population

- **Inclusion Criteria:**
    1. Adult patients (≥18 years) at ICU admission
    2. First (index) ICU admission during hospitalization

3. At least one arterial blood gas measurement with PaO□ and PaCO□
4. Available SpO□ and MAP during ICU stay
5. Documented ICU discharge status

- **Exclusion Criteria:**
  1. Age <18 years
  2. Missing or non-numeric PaO□ or PaCO□ values
  3. Missing ICU outcome data
  4. Physiologically implausible ABG values
  5. ECMO during ABG measurement (if identifiable)
  6. No SpO□ or MAP measurements during ICU stay
  7. Repeat ICU admissions beyond index stay
  8. DNR/comfort-care orders prior to ABG measurement (optional for sensitivity analyses)

5. Data Collection and Variables

- **Exposure Variable:** PaO□/PaCO□ ratio (calculated from ABG measurements)
- **Outcome Variable:** ICU mortality (yes/no)
- **Covariates for Adjustment:**
  - Oxygen saturation (SpO□)
  - Mean arterial pressure (MAP)
  - Age, sex, ICU type (medical/surgical), comorbidities (if available)
  - Mechanical ventilation status
- **Time Points:** First ABG per ICU stay (primary), or median/peak ABG values for sensitivity analysis

6. Statistical Analysis Plan (SAP)

6.1 Descriptive Analysis

- Continuous variables: mean ± SD or median (IQR)

- Categorical variables: counts and percentages
- Compare baseline characteristics across PaO□/PaCO□ quartiles using ANOVA/Kruskal-Wallis for continuous variables and chi-square/Fisher's exact test for categorical variables

6.2 Primary Analysis

- **Model:** Multivariable logistic regression
- **Dependent Variable:** ICU mortality (binary)
- **Independent Variable:** PaO□/PaCO□ ratio (continuous or categorical)
- **Covariates:** SpO□, MAP, age, sex, ICU type, comorbidities
- **Effect Measures:** Adjusted odds ratios (ORs) with 95% confidence intervals
- **Assessment of Independence:** Evaluate whether PaO□/PaCO□ remains statistically significant after adjustment

6.3 Secondary Analyses

- **Subgroup Analyses:** Mechanical ventilation status, age categories, ICU type
- **Sensitivity Analyses:**
    - Excluding extreme ABG values
    - Excluding DNR/comfort-care patients
    - Using alternative PaO□/PaCO□ calculation methods (first ABG vs. median ABG)
- **Time-to-event Analysis (Optional):** Cox proportional hazards for ICU length of stay, treating death as event

6.4 Missing Data Handling

- Exclude patients missing primary exposure or outcome
- For covariates (SpO□, MAP, comorbidities):
    - If <5% missing: complete-case analysis
    - If >5% missing: consider multiple imputation

6.5 Statistical Software

- R (version ≥4.0) or STATA (version ≥16)
- Two-sided p-value <0.05 considered statistically significant

7. Ethical Considerations

- Secondary analysis of **de-identified public data (MIMIC-II)**
- No new patient consent required
- Approved by MIT and Beth Israel Deaconess Medical Center Institutional Review Boards for public data use

8. Reporting

- Follow **STROBE guidelines** for observational studies
- Present baseline tables, regression results, and flowchart of included/excluded patients
- Include sensitivity and subgroup analyses
- Report odds ratios, 95% CI, and p-values