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The association between intraoperative perfusion index, heart rate and mortality: a protocol for an observational study

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Statistical Analysis Plan

Objectives & estimands

- **Primary objective:** Estimate the causal effect of intraoperative low perfusion index (PI) on 30-day all-cause mortality.
- **Primary estimand:** Adjusted odds ratio (OR) for 30-day mortality per increase in cumulative exposure to PI< 1.5 (area-under-threshold, AUT; units %·min).
- **Secondary estimands:**
    - Association of mean intraoperative PI with 30-day mortality.
    - Same estimands for the composite outcome (ICU admission, acute kidney injury according to Kidney Disease: Improving Global Outcome (KDIGO) criteria (≥1.5-fold increase from baseline within 7 days after surgery or 0.3mg dl^{-1} increase within 48h), reoperation ≤30 days, or prolonged LOS [≥75th percentile within surgery category]).
    - Associations for alternative AUT thresholds (0.5, 2.0, 3.0, 4.0, 5.0).
    - Effect modification by MAP exposure, ASA score, and urgency (acute vs elective).

Study population & analysis sets

- **Source cohort:** Adults (≥18y) undergoing general anesthesia Jan-2017 to Dec-2024 in Capital & Zealand Regions (OPIAID database).
- **Inclusion/exclusion:** As in Methods (non-cardiac surgery; exclude missing PI, missing 30-day status).
- **Index surgery:** If a patient has multiple eligible procedures within 30 days, analysis uses the first eligible surgery.

Time origin & exposure window

- **Time zero:** first incision.
- **Exposure window:** incision → last suture (intraoperative period). Data outside this window are excluded.

Exposure definitions

1. **Primary exposure:** AUT <1.5 (%·min).
2. **Secondary exposures:**
    - Mean PI across intraoperative period.
    - AUT <0.5, <2.0, <3.0 (%·min).

Scaling: AUT terms analyzed per 100 %·min (primary) and, if helpful, per 10 %·min in figures. Mean PI analyzed per 1 PI unit.

Outcomes

- **Primary outcome:** 30-day all-cause mortality (binary).
- **Secondary outcome:** composite outcome (binary). Components also reported descriptively and as exploratory models.

Confounding control

Primary adjustment set: Age, sex, ASA score, Charlson comorbidity index, intraoperative heart rate, intraoperative MAP, and urgency of surgery. Additional sensitivity analyses will explore robustness to expanded adjustment sets including intraoperative fluids and blood product transfusions, vasopressor use, hospital, surgical duration, and anesthesia type.

Data preprocessing & quality rules (prespecified)

- Remove physiologically implausible values: PI <0 or >20, HR <25 or >250 bpm, MAP <15 or >150 mmHg.
- Interpolation: linear interpolation for gaps ≤5 min.
- For >5–15 min gaps: Missingness indicator.
- Exclude records with >50% missing intraop monitoring relative to surgical time; sensitivity evaluates impact of this threshold.

Primary analysis

- **Model:** multivariable logistic regression of 30-day mortality on AUT <1.5 plus the primary adjustment set.
- **Functional form:** restricted cubic splines (RCS) for AUT<1.5.
- **Estimation:** two-sided α=0.05; report overall association.
- **Effect presentation:**
    - **Dose–response plot**: adjusted OR vs AUT with 95% CI.
    - Tabulate ORs at clinically relevant AUT values.

Secondary analyses

1. **Mean PI models** (crude spline visualization, then adjusted linear/spline as above).
2. **Composite outcome** with identical specifications.
3. **Alternative thresholds**: repeat primary spline model with AUT <0.5, 2.0, 3.0
4. **Specialty and risk subgroups**: fit the same primary model within strata of surgical specialty; same-day surgery vs overnight; acute vs elective.
5. **Effect modification:** include interaction terms:
    - AUT<1.5 × AUT<65 mmHg (MAP),
    - AUT<1.5 × ASA,
    - AUT<1.5 × urgency.

Sensitivity analyses (robustness)

- **Alternative adjustment sets:** intraoperative fluids/transfusion, vasopressors, hospital (fixed) or random intercept, anesthesia type, surgery duration.
- **Monitoring influence:** exclude sites where PI may have guided therapy.

Reporting

- Effect sizes as ORs with 95% CIs.
- Figures:
    1. Adjusted spline dose–response (OR vs AUT<1.5).
    2. Subgroup/interaction spline panels where relevant.
- Tables: cohort characteristics by mortality status; model coefficients.

Software & reproducibility

- Analyses in R (latest stable).