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Intraoperative Inspired Oxygen Exposure and Mechanical Ventilation Recorded 24–48 Hours After Intracranial Neurosurgery: An INSPIRE Cohort Study

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Abstract

Background

The optimal intraoperative inspired oxygen concentration remains uncertain. We examined whether greater inspired oxygen exposure was associated with mechanical ventilation being recorded during postoperative hours 24–48 after intracranial neurosurgery.

Methods

This retrospective cohort study used the publicly available INSPIRE perioperative database. Adults undergoing major intracranial surgery under general anaesthesia were included when surgery lasted at least 120 min, intraoperative mechanical ventilation was independently documented, and paired FiO_2–SpO_2 data covered at least 80% of the operative interval. The exposure was time-weighted average excess oxygen exposure (TWAEO), calculated as inspired oxygen above 21% during intervals with SpO_2 >92%, divided by valid paired observation time. TWAEO quantifies inspired oxygen administration during adequate pulse-oximetry saturation, not arterial hyperoxaemia. The outcome was at least one postoperative vent = 1 record during hours 24–48. Missing covariates were handled using 50 chained-equation imputations with predictive mean matching.

Results

Among 1,602 patients, 98 (6.1%) met the primary outcome. Each 10-percentage-point increase in TWAEO was associated with greater adjusted odds of a ventilation record at 24–48 h (odds ratio [OR], 1.54; 95% confidence interval [CI], 1.18–2.02). Auditing classified 81 events as continued-supported, 15 as reinitiation/reintubation-like, and two as indeterminate. Restriction to the 81 continued-supported events yielded an OR of 1.72 (95% CI, 1.27–2.33), although the records could not confirm continued invasive ventilation. Additional adjustment for intraoperative ventilation strategy attenuated the estimate to 1.31 (95% CI, 0.98–1.74). TWAEO was nearly collinear with mean FiO_2 (r = 0.99994), and the spline analysis provided no evidence of non-linearity (P=.587).

Conclusions

Greater inspired oxygen exposure was associated with mechanical ventilation being recorded at 24–48 h. The findings do not establish causality, a clinical oxygen target, or superiority of TWAEO over mean FiO_2.

Background

Postoperative respiratory support after intracranial surgery is clinically consequential because delayed recovery of consciousness, impaired airway reflexes, neurological injury, long operations, blood loss, and pulmonary dysfunction can all influence readiness for extubation and the subsequent need for ventilatory assistance. In a large neurosurgical registry, postoperative respiratory failure—defined as unplanned intubation or ventilator dependence for more than 48 h—occurred in 2.5% of procedures and was associated with patient vulnerability and cranial rather than spinal surgery [1]. Smaller intracranial cohorts have likewise shown that postoperative reintubation and prolonged ventilation are accompanied by pulmonary complications and longer intensive-care and hospital stays [2, 3]. These observations make potentially modifiable intraoperative respiratory exposures relevant, while also highlighting that postoperative ventilation is strongly confounded by neurological and procedural severity.

Supplemental oxygen is routinely administered during general anaesthesia to increase safety during airway manipulation and to preserve arterial oxygenation. Its optimal intraoperative concentration, however, remains unresolved. High FiO_2 may increase oxygen reserve and has been studied as a strategy to reduce surgical-site infection, but randomized trials have not demonstrated consistent benefit and were generally not designed to detect small differences in non-infectious respiratory outcomes [4]. Conversely, high inspired oxygen may promote absorption atelectasis and oxidative injury. Large observational studies have associated higher intraoperative FiO_2 with major respiratory complications [5], and a multicentre cohort of 350,647 patients linked cumulative supraphysiological oxygen exposure during adequate saturation with postoperative kidney, myocardial, and lung injury [6]. A recent prospective multicentre cohort reported a similar exposure approach for pulmonary complications after abdominal surgery [11]. Other cohorts have reported little or no association with broader recovery outcomes, underscoring continuing uncertainty and the potential influence of confounding by indication [7].

Existing work on postoperative ventilation after intracranial surgery has focused mainly on patient, neurological, and operative predictors. Neurocritical-care studies have emphasized consciousness, airway protection, secretion burden, illness severity, and institutional practice when evaluating extubation readiness and failure [12–16]. A recent elective intracranial cohort defined prolonged postoperative mechanical ventilation as ventilation beyond 48 h, but included only 12 events among 273 patients [3]. Whether continuously quantified intraoperative inspired oxygen exposure is associated with later postoperative ventilation records in a larger intracranial neurosurgical population remains poorly characterized.

We therefore used the INformative Surgical Patient dataset for Innovative Research Environment (INSPIRE), which contains granular perioperative time-series data [8, 9], to quantify inspired oxygen administered above room air during intervals of adequate SpO_2. We hypothesized that greater time-weighted average excess oxygen exposure would be associated with a higher likelihood of mechanical ventilation being recorded during postoperative hours 24–48. This exposure captures inspired oxygen administration rather than arterial hyperoxaemia. Because the public outcome field does not identify the

airway device, extubation time, or invasive versus non-invasive mode, we used cautious outcome wording and audited the temporal pattern of postoperative ventilation records.

Methods

Study design and data source

We conducted a retrospective cohort study using INSPIRE version 1.4.2, a publicly available, de-identified perioperative database derived from Seoul National University Hospital. INSPIRE includes operation-level information, diagnoses, laboratory values, medications, intraoperative physiological time series, and postoperative ward observations from surgical care delivered between 2011 and 2020 [8, 9]. The source dataset was approved for public release by the Seoul National University Hospital Institutional Review Board, with informed consent waived because of the retrospective design, and by the institutional data review board after assessment of anonymisation [8]. This secondary analysis used only de-identified data governed by the PhysioNet data-use agreement.

The study is reported in accordance with the STROBE recommendations for observational studies [10]. A feasibility phase initially evaluated 90-day mortality as the principal outcome. After feasibility analyses showed no clear adjusted mortality association but a gradient in postoperative ventilation records, the primary outcome was amended to a ventilation record at 24–48 h. The amendment preceded formal MICE modelling, restricted cubic-spline analysis, and the protocol-defined sensitivity analyses reported here. No oxygen-exposure threshold was selected from the outcome data. Supplementary Methods S1 describes the formal-analysis amendment and outcome-selection sequence.

Cohort selection

Candidate operations were identified among adults in the neurosurgery department who received general anaesthesia and had a positive recorded operation duration. Major intracranial surgery was defined using the curated five-character ICD-10-PCS codes and code groups listed in Supplementary Table S4. Independent intraoperative mechanical-ventilation evidence required at least one tidal-volume value of 50–2,000 mL, PEEP value of 0–30 cmH_2O, or minute-ventilation value of 0.1–30 L/min during the operative interval.

Among 3,891 candidate major intracranial operations, 2,367 lasted at least 120 min, excluding 1,524 shorter operations. Of these, 1,772 had independent evidence of intraoperative mechanical ventilation and valid FiO_2 and SpO_2 records, excluding 595 operations. Paired data covered at least 80% of the recorded operative interval in 1,752 operations, excluding 20. We excluded three operations with two consecutive 5-min epochs at SpO_2 <90% or SpO_2 <90% during at least 5% of valid paired time, leaving 1,749 eligible operations. We then retained only the first eligible operation for each patient, excluding 147 repeat procedures. The final cohort comprised 1,602 patients and operations (Fig. 1).

Exposure definition

The primary exposure was time-weighted average excess oxygen exposure (TWAEO), adapted from the supraphysiological oxygen area-under-the-curve approach described by McIlroy and colleagues [6]. FiO_2 was expressed as a percentage, and time was expressed in minutes. At each paired observation, excess oxygen was defined as max(FiO_2−21, 0) when the corresponding SpO_2 was > 92%, and as zero otherwise. Each observation contributed no more than 5 min, and the denominator was total valid paired FiO_2–SpO_2 observation time. TWAEO was calculated as:

TWAEO = Σ[max(FiO_2−21, 0) × Δt × I(SpO_2>92%)] / paired valid time.

TWAEO has units of percentage points and quantifies inspired oxygen administration above room air during adequate pulse-oximetry saturation. It is not a measure of arterial hyperoxaemia because arterial oxygen tension was unavailable. The primary effect estimate was reported per 10-percentage-point increase in TWAEO, approximately corresponding to the interquartile exposure difference in this cohort. Protocol-defined alternative exposure definitions specified before formal modelling included an SpO_2 threshold of > 96%, accumulation only when FiO_2 was > 40% and SpO_2 >92%, excess FiO_2 above 50% while SpO_2 was > 96%, the percentage of time meeting FiO_2 >50% and SpO_2 >96%, the unstandardized excess-oxygen area under the curve, mean FiO_2, and a window excluding the first and last 15 min of surgery.

Outcomes

The primary outcome was at least one observation in ward_vitals with item_name="vent" and value = 1 during postoperative hours 24–48, measured from recorded operation end. INSPIRE version 1.4.2 derives the ventilation field using information that can include PEEP, ventilator mode, BIPAP mode, and the Glasgow Coma Scale verbal component [9]. The public tables do not provide a dedicated airway-device field, extubation timestamp, or a definitive invasive/non-invasive classification. Accordingly, the primary outcome is described as mechanical ventilation recorded during postoperative hours 24–48, not as delayed extubation, prolonged invasive mechanical ventilation, or confirmed continuous ventilation.

We audited all primary events using earlier postoperative ventilation records. A continued-supported outcome pattern required vent = 1 within 6 h after surgery and no vent = 0 observation before the first positive record during hours 24–48. A vent = 0 record before a later 24–48 h positive record was classified as a reinitiation/reintubation-like pattern; remaining events were classified as indeterminate. The same logic was applied to postoperative hours 48–72. Thirty- and 90-day mortality were evaluated as secondary outcomes.

Covariates

The primary model was selected to control major baseline and procedural sources of confounding while preserving an adequate events-per-parameter ratio. Covariates were age per 10 years, sex, American Society of Anesthesiologists (ASA) physical-status class modelled ordinally per one-class increase, emergency status, haemorrhage/decompression procedure category, operation duration per hour, body mass index (BMI) per 5 kg/m², and percentage of valid intraoperative time with SpO_2 <92%. Together with TWAEO, the model contained nine non-intercept parameters. Ventilation-strategy sensitivity adjustment additionally included median PEEP, median tidal volume per predicted body weight (VT/PBW), and dynamic driving pressure. A further model added estimated blood loss, red-cell transfusion, fluid administration rate, and any vasopressor record.

Missing data

ASA class was missing for 59 patients (3.7%) and BMI for 42 (2.6%). Missingness in ventilation-strategy covariates was greater, including 280 patients (17.5%) for PEEP and dynamic driving pressure and 20 (1.2%) for VT/PBW. The exposure and outcomes were complete by cohort definition and were not imputed. The primary analysis used multiple imputation by chained equations (MICE) with predictive mean matching, 50 imputed datasets, 10 iterations, and a fixed random seed. The observed outcome and exposure were included as predictors in the imputation model, together with primary covariates and auxiliary intraoperative variables. Coefficients and variances were combined using Rubin's rules. Complete-case analysis was retained as a sensitivity analysis; it included 1,504 patients but only 70 primary events.

Statistical analysis

Continuous variables are summarized as mean (standard deviation) or median [interquartile range], as appropriate, and categorical variables as number (percentage). Logistic regression was used to estimate ORs and 95% CIs. Model progression included crude, age-and-sex adjusted, clinical-severity adjusted, and fully adjusted models. Model 1 included age and sex. The clinical-severity model additionally included ASA class, emergency status, haemorrhage/decompression category, and operation duration. The fully adjusted primary model further included BMI and the percentage of valid intraoperative time with SpO_2 <92%. With 98 primary events and nine non-intercept parameters, the main model had 10.9 events per parameter.

TWAEO was also analyzed in fixed quartiles selected during feasibility work; quartile estimates were treated as descriptive secondary analyses rather than threshold tests. A three-knot restricted cubic spline with knots at the 10th, 50th, and 90th percentiles assessed overall association and non-linearity. Sensitivity analyses examined alternative exposure definitions, paired-data coverage ≥ 90%, elective surgery only, exclusion of haemorrhage/decompression procedures, the trimmed operative window, audited continued-supported outcomes at 24–48 and 48–72 h, and the expanded covariate models described above. Because these analyses evaluated consistency rather than independent hypotheses, their pattern, effect estimates, and precision were emphasized rather than a binary significance count.

In the same complete-case sample, TWAEO and mean FiO_2 were compared using Pearson correlation, Akaike information criterion (AIC), and the c-statistic. They were not entered together because of near-perfect collinearity. Tests were two-sided. Formal analyses were performed using reproducible custom scripts in Python 3.12 with a fixed random seed; the archived analysis package contains the complete code and publication-facing outputs.

Results

Cohort and exposure distribution

The cohort included 1,602 patients with a mean age of 53.6 years; 738 (46.1%) were men and 234 (14.6%) underwent emergency surgery. Procedures comprised 1,344 (83.9%) Tumor/skull-base, 29 (1.8%) Cerebrovascular, 224 (14.0%) Hemorrhage/decompression, and five (0.3%) Other intracranial operations (Table 1). Median operation duration was 235 [175–305] min. Median TWAEO was 24.0 [15.0–25.1] percentage points, median intraoperative FiO_2 was 45.0% [36.0–46.0%], and median SpO_2 was 100% [100–100%]. Exposure values were strongly heaped: 34.1% of patients had TWAEO between 24 and < 26 percentage points (Fig. 2A).

Table 1
Selected cohort characteristics overall and by TWAEO quartile

Characteristic	Overall	Q1	Q2	Q3	Q4
Patients, n	1,602	403	412	386	401
Age, years, mean (SD)	53.6 (14.7)	52.6 (15.0)	51.8 (15.3)	54.1 (14.2)	56.1 (14.2)
Male sex, n (%)	738 (46.1)	207 (51.4)	236 (57.3)	160 (41.5)	135 (33.7)
BMI, kg/m², mean (SD)	23.9 (3.8)	24.1 (3.5)	24.7 (3.8)	23.3 (3.7)	23.4 (3.8)
ASA ≥ III, n (%)	223 (14.5)	53 (13.4)	54 (13.5)	46 (12.4)	70 (18.6)
Emergency surgery, n (%)	234 (14.6)	39 (9.7)	63 (15.3)	56 (14.5)	76 (19.0)
Tumor/skull-base procedure, n (%)	1,344 (83.9)	364 (90.3)	341 (82.8)	331 (85.8)	308 (76.8)
Cerebrovascular procedure, n (%)	29 (1.8)	0 (0.0)	4 (1.0)	9 (2.3)	16 (4.0)
Haemorrhage/decompression procedure, n (%)	224 (14.0)	38 (9.4)	65 (15.8)	46 (11.9)	75 (18.7)
Other intracranial procedure, n (%)	5 (0.3)	1 (0.2)	2 (0.5)	0 (0.0)	2 (0.5)
Operation duration, min	235 [175–305]	215 [165–280]	228 [175–290]	248 [185–325]	250 [180–325]
TWAEO, percentage points	24.0 [15.0–25.1]	11.0 [1.8–13.2]	21.2 [17.6–22.8]	25.0 [24.7–25.0]	26.3 [25.7–28.0]
Median FiO_2, %	45.0 [36.0–46.0]	32.0 [22.4–34.0]	42.0 [37.0–44.0]	46.0 [46.0–46.0]	47.0 [46.0–49.0]
Median SpO_2, %	100 [100–100]	100 [99–100]	100 [100–100]	100 [100–100]	100 [100–100]
Median PEEP, cmH_2O	5.0 [5.0–5.0]	5.0 [5.0–6.0]	5.0 [5.0–5.0]	5.0 [2.2–5.0]	5.0 [0.0–5.0]
Median VT/PBW, mL/kg	7.8 [7.2–8.5]	7.5 [7.1–8.0]	7.6 [7.1–8.2]	8.0 [7.3–8.8]	8.1 [7.4–9.0]
Ventilation record at 24–48 h, n (%)	98 (6.1)	7 (1.7)	13 (3.2)	34 (8.8)	44 (11.0)
Continued-supported pattern at 24–48 h, n (%)	81 (5.1)	5 (1.2)	10 (2.4)	27 (7.0)	39 (9.7)

Characteristic	Overall	Q1	Q2	Q3	Q4
90-day mortality, n (%)	70 (4.4)	13 (3.2)	14 (3.4)	20 (5.2)	23 (5.7)

Values are median [interquartile range] unless otherwise indicated. Percentages for ASA ≥ III use patients with recorded ASA class as the denominator; ASA was missing for 59 patients overall (Q1, 7; Q2, 11; Q3, 16; Q4, 25). BMI also contained missing values before imputation. ASA, American Society of Anesthesiologists physical-status class; TWAEO, time-weighted average excess oxygen exposure.

Primary outcome and audit

Mechanical ventilation was recorded during postoperative hours 24–48 in 98 patients (6.1%). Outcome auditing identified a continued-supported pattern in 81 of the 98 events (82.7%), a reinitiation/reintubation-like pattern in 15 (15.3%), and an indeterminate pattern in two (2.0%) (Table 2; Fig. 2C). Thus, most events were temporally compatible with an uninterrupted postoperative ventilation course, although the source data could not confirm invasive ventilation or an unbroken airway-device pathway.

Table 2
Audit of the postoperative ventilation outcome

Definition	n	Interpretation
Strict cohort	1,602	Denominator
Any vent = 1 during 24–48 h	98	Primary outcome
Early vent = 1 within 6 h and no prior vent = 0	81	Supports a continued ventilation course
vent = 0 before a later vent = 1	15	Supports reinitiation/reintubation-like course
No early positive record or zero-to-one transition	2	Indeterminate
Any vent = 1 during 48–72 h	79	Secondary window
Continued-supported pattern during 48–72 h	64	Audited secondary outcome

The ventilation field may include BIPAP-derived detection and cannot establish invasive ventilation or an airway-device trajectory.

Primary association

In the primary MICE model, each 10-percentage-point increase in TWAEO was associated with greater odds of a ventilation record during postoperative hours 24–48 (adjusted OR, 1.54; 95% CI, 1.18–2.02; P=.0017) (Table 3). The crude OR was 1.90 (95% CI, 1.50–2.41), and progressive covariate adjustment attenuated the estimate. Other model coefficients were directionally consistent with major clinical

severity gradients: emergency surgery had an OR of 5.26 (95% CI, 2.30–12.00), haemorrhage/decompression an OR of 2.35 (95% CI, 1.02–5.40), and each additional operation hour an OR of 1.64 (95% CI, 1.45–1.86). Complete-case analysis yielded an OR of 1.74 (95% CI, 1.27–2.40).

Table 3
Model progression and primary association

Model	OR per 10 TWAEO points	95% CI	P value	n/events
Crude	1.90	1.50–2.41	< .001	1,602/98
Age and sex adjusted	1.81	1.43–2.29	< .001	1,602/98
Clinical-severity adjusted	1.55	1.19–2.01	.001	1,602/98
Primary MICE adjusted	1.54	1.18–2.02	.0017	1,602/98
Complete-case adjusted	1.74	1.27–2.40	< .001	1,504/70

The primary model adjusted for age, sex, ASA class, emergency status, haemorrhage/decompression, operation duration, BMI, and intraoperative SpO_2 <92% burden. MICE, multiple imputation by chained equations.

Observed outcome rates were 1.74%, 3.16%, 8.81%, and 10.97% from the first through fourth TWAEO quartiles. Relative to the first quartile, adjusted ORs were 1.53 (95% CI, 0.57–4.10) for the second, 5.11 (95% CI, 2.07–12.62) for the third, and 5.08 (95% CI, 2.09–12.33) for the fourth (Fig. 2B). The third quartile covered a narrow range (24.01–25.12 percentage points) because of exposure heaping. Restricted cubic-spline analysis supported an overall association (P=.008) but provided no evidence of non-linearity (P=.587) (Fig. 3). The quartiles are descriptive and these findings do not identify a discrete oxygen-exposure threshold.

Sensitivity analyses

The direction of association was consistent when excess oxygen was accumulated only at SpO_2 >96% (OR, 1.66; 95% CI, 1.23–2.24), when accumulation required FiO_2 >40% with SpO_2 >92% (OR, 1.64; 95% CI, 1.15–2.34), and when paired-data coverage was restricted to ≥ 90% (OR, 1.54; 95% CI, 1.17–2.01) (Table 4; Fig. 4). Estimates remained elevated in elective-only surgery (OR, 1.81; 95% CI, 1.13–2.90; 42 events), after exclusion of haemorrhage/decompression procedures (OR, 1.74; 95% CI, 1.11–2.74; 47 events), and after removing the first and last 15 min of the operative window (OR, 1.55; 95% CI, 1.19–2.03). The restricted-cohort analyses were interpreted as consistency checks because of their smaller event counts.

Restricting the primary outcome to the 81 continued-supported patterns produced an OR of 1.72 (95% CI, 1.27–2.33). A continued-supported outcome at 48–72 h was present in 64 patients and remained associated with TWAEO (OR, 1.49; 95% CI, 1.08–2.06), whereas the less specific outcome of any ventilation record at 48–72 h had an OR of 1.29 (95% CI, 0.97–1.71).

Not all sensitivity analyses were equally supportive. The estimate was attenuated after additional adjustment for PEEP, VT/PBW, and dynamic driving pressure (OR, 1.31; 95% CI, 0.98–1.74; P=.064). Adjustment for blood loss, red-cell transfusion, fluid rate, and vasopressor records yielded an OR of 1.34 (95% CI, 1.01–1.77). A stricter FiO_2 >50% and SpO_2 >96% excess definition had an OR of 1.18 (95% CI, 0.69–2.01), and the corresponding exposure-time proportion had an OR of 1.11 (95% CI, 0.99–1.25).

Table 4
Protocol-defined sensitivity analyses and secondary outcome analyses

Analysis	OR	95% CI	n/events
Primary MICE	1.54	1.18–2.02	1,602/98
SpO_2 >96% definition	1.66	1.23–2.24	1,602/98
FiO_2 >40% while SpO_2 >92%	1.64	1.15–2.34	1,602/98
FiO_2 >50% while SpO_2 >96% excess	1.18	0.69–2.01	1,602/98
Percent time FiO_2 >50% and SpO_2 >96%	1.11	0.99–1.25	1,602/98
Paired-data coverage ≥ 90%	1.54	1.17–2.01	1,592/96
Elective surgery only	1.81	1.13–2.90	1,368/42
Excluding haemorrhage/decompression	1.74	1.11–2.74	1,378/47
Trimmed operative window	1.55	1.19–2.03	1,602/98
Continued-supported 24–48 h	1.72	1.27–2.33	1,602/81
Any ventilation record 48–72 h	1.29	0.97–1.71	1,602/79
Continued-supported 48–72 h	1.49	1.08–2.06	1,602/64
Ventilation-strategy adjusted	1.31	0.98–1.74	1,602/98
Bleeding/fluid/vasopressor adjusted	1.34	1.01–1.77	1,602/98
90-day mortality	1.25	0.93–1.67	1,602/70

ORs are per 10-percentage-point increase in the named exposure, except the time-proportion analysis, which follows its protocol-defined scaling. Each model used the primary adjustment set except where the analysis label indicates additional covariates or a restricted cohort.

Comparison with mean FiO_2 and mortality

Because SpO_2 was almost uniformly maintained at 100%, TWAEO was nearly perfectly correlated with mean FiO_2 (r = 0.99994). In the complete-case sample, adding TWAEO to the covariate model changed the AIC from 478.33 to 468.19 and the c-statistic from 0.846 to 0.859; adding mean FiO_2 produced an AIC of 468.12 and the same c-statistic of 0.859. Per 10-percentage-point increase, mean FiO_2 yielded

essentially the same adjusted association as TWAEO (OR, 1.54; 95% CI, 1.18–2.02). Thus, the data do not support superiority of TWAEO over mean FiO_2 in this cohort.

No clear association was observed with 90-day mortality (70 events; OR, 1.25; 95% CI, 0.93–1.67) or 30-day mortality (31 events; OR, 1.33; 95% CI, 0.92–1.93).

Discussion

Principal findings

In this retrospective cohort of 1,602 adults undergoing major intracranial surgery, greater intraoperative inspired oxygen exposure quantified by TWAEO was associated with a higher likelihood of mechanical ventilation being recorded during postoperative hours 24–48. The estimate was consistent across several restrictions intended to reduce confounding by urgency, haemorrhage/decompression surgery, exposure-window selection, and incomplete FiO_2–SpO_2 coverage. Auditing the outcome showed that most events were compatible with an uninterrupted postoperative ventilation course, and restriction to this more specific temporal pattern yielded a similar, slightly stronger estimate. A continued-supported outcome at 48–72 h also showed an association.

The findings nevertheless require a deliberately narrow interpretation. Additional adjustment for PEEP, VT/PBW, and dynamic driving pressure attenuated the OR from 1.54 to 1.31 and moved the 95% CI across one. This attenuation suggests that inspired oxygen concentration may partly act as a marker of broader intraoperative respiratory management, pulmonary mechanics, clinical concern, or underlying physiological vulnerability. The result therefore does not establish FiO_2 as an independent causal risk factor and does not show that lowering FiO_2 would reduce postoperative ventilation.

Relation to previous work

Our results extend, but do not replicate, previous perioperative oxygen studies. Staehr-Rye and colleagues reported a dose-dependent association between higher median intraoperative FiO_2 and a composite of major respiratory complications in 73,922 non-cardiothoracic procedures [5]. McIlroy and colleagues subsequently quantified cumulative FiO_2 above 21% during adequate saturation and found associations with postoperative kidney, myocardial, and lung injury across 350,647 procedures [6]. The present study applies the same conceptual exposure approach to a focused intracranial neurosurgical population and a respiratory-support-related postoperative outcome. The absence of a clear mortality association in our data is compatible with the small and imprecise mortality estimate in the multicentre BMJ cohort and with the lack of association between mean FiO_2 and days alive and out of hospital at 90 days in another elective surgical cohort [6, 7].

The neurosurgical literature also emphasizes why outcome terminology matters. Cote and colleagues used a validated clinical composite of unplanned intubation and ventilator dependence beyond 48 h [1]. Hayashi and colleagues prospectively assessed extubation and reintubation pathways [2], and the recent

elective intracranial cohort explicitly separated operating-room extubation, ICU extubation within 48 h, and ventilation beyond 48 h [3]. INSPIRE does not expose equivalent airway-device or extubation timestamps. Our primary outcome is therefore broader and less clinically specific than conventional prolonged postoperative mechanical ventilation. Its value lies in reproducible ascertainment and temporal auditing, not in substituting for a confirmed extubation endpoint.

Interpretation

Several mechanisms could generate the observed pattern, but none can be established by this analysis. Greater inspired oxygen exposure could contribute to absorption atelectasis, altered pulmonary mechanics, or oxidative injury, which may influence postoperative respiratory support. Alternatively, clinicians may select higher FiO_2 for patients perceived to have poorer pulmonary reserve, more complex operations, haemodynamic instability, or emerging intraoperative problems. The strong associations of emergency status, haemorrhage/decompression, and operation duration with the outcome, together with attenuation after ventilation-strategy adjustment, support substantial confounding by indication and severity. Postoperative neurological status, airway protection, sedation, and institutional extubation practices may also determine ventilation records independently of lung injury.

TWAEO should likewise be interpreted as an exposure summary rather than a biomarker or a measure of arterial hyperoxaemia. The metric was intended to count inspired oxygen above room air only during adequate saturation, thereby separating liberal oxygen administration from treatment of overt desaturation. In this cohort, however, median SpO_2 was 100% and clinically important desaturation was uncommon. Consequently, the saturation condition removed little observation time, making TWAEO mathematically close to mean FiO_2 minus 21 percentage points. Their correlation, model fit, discrimination, and effect estimates were essentially identical. The data therefore do not support superiority of TWAEO over mean FiO_2.

The quartile results also should not be read as evidence of a threshold near 25 percentage points. More than one-third of the cohort clustered between 24 and < 26 points. This heaping may reflect routine FiO_2 settings and the privacy-preserving coarsening of continuous measurements in the public INSPIRE release. The nearly identical third- and fourth-quartile ORs arose in groups with markedly different widths, and the spline test did not support non-linearity. Accordingly, the continuous estimate is the primary result, and the quartile pattern is descriptive.

Strengths and limitations

Strengths include a specialist intracranial neurosurgical cohort, continuous paired FiO_2–SpO_2 measurements, time-weighted exposure quantification, a model sized to the available event count, preservation of all 1,602 patients through multiple imputation, a transparent outcome audit, and sensitivity analyses that addressed emergency surgery, haemorrhage/decompression, operative-window selection, data coverage, later outcome windows, and broader intraoperative management.

The study also has important limitations. First, ward_vitals.vent may incorporate PEEP, ventilator mode, BIPAP mode, and neurological documentation; it cannot distinguish invasive from non-invasive support or provide extubation and reintubation timestamps. Although 81 of 98 events supported a continued temporal course, they cannot be called confirmed continued invasive ventilation. Second, this single-centre retrospective database study is vulnerable to residual confounding, particularly confounding by indication. Relevant factors such as detailed pulmonary disease, arterial oxygen tension, postoperative neurological examination, airway-protection assessment, sedation, clinician intent, extubation protocol, and postoperative complications were incompletely measured or unavailable. Third, the ventilation-strategy model had more missingness and fewer events per parameter, but its attenuation remains a central caution. Fourth, TWAEO offered no measurable advantage over mean FiO_2 because SpO_2 was nearly uniform. Fifth, the requirement for operations lasting at least 120 min and high-density paired FiO_2–SpO_2 data restricted the analysis to patients with sufficiently detailed intraoperative monitoring. This selection may limit generalisability to shorter or less intensively monitored intracranial procedures. Selection bias related to the availability of high-quality intraoperative monitoring data cannot be excluded. Sixth, the public INSPIRE release applies privacy-preserving processing to continuous measurements: values below and above the 2.5th and 97.5th percentiles are truncated, and remaining values are mapped to the nearest 5th-percentile value [8, 9]. This coarsening may have contributed to exposure heaping and limits fine-scale threshold interpretation. Seventh, the primary outcome was selected after feasibility analyses rather than at project inception; although it was frozen before formal imputation, spline modelling, and protocol-defined sensitivity analyses, independent validation is especially important. Eighth, the event count limited interaction analyses and the precision of elective-only and exclusion subgroups. Finally, multiple sensitivity analyses were performed, and their results should be understood as a consistency pattern rather than independent confirmatory tests.

Implications

These findings identify a testable association, not a clinical oxygen target. Replication should use datasets containing airway-device status, explicit extubation and reintubation times, invasive and non-invasive ventilation modes, arterial oxygen measurements, detailed respiratory comorbidity, neurological status, and clinician-recorded indications. A prospectively specified multicentre study could determine whether the association persists under better control of confounding and whether any signal is mediated by postoperative pulmonary dysfunction. Interventional oxygen titration should be considered only after observational replication and with safeguards against hypoxaemia.

Conclusions

Greater intraoperative inspired oxygen exposure quantified by TWAEO was associated with a higher likelihood of mechanical ventilation being recorded during postoperative hours 24–48 after intracranial neurosurgery. The association was consistent across several cohort and outcome-audit analyses but attenuated after additional adjustment for intraoperative ventilation strategy. Because the data could not distinguish invasive from non-invasive support or uninterrupted from reinitiated ventilation, and because

residual confounding is likely, the findings should be interpreted as associative and hypothesis-generating rather than causal. No discrete oxygen-exposure threshold was identified.

Abbreviations

AIC
Akaike information criterion
ASA
American Society of Anesthesiologists
BIPAP
bilevel positive airway pressure
BMI
body mass index
CI
confidence interval
FiO_2
fraction of inspired oxygen
INSPIRE
INformative Surgical Patient dataset for Innovative Research Environment
MICE
multiple imputation by chained equations
OR
odds ratio
PBW
predicted body weight
PEEP
positive end-expiratory pressure
RCS
restricted cubic spline
SpO_2
peripheral oxygen saturation
TWAEO
time-weighted average excess oxygen exposure
VT
tidal volume.

Declarations

Ethics approval and consent to participate

The INSPIRE source study was approved by the Institutional Review Board of Seoul National University Hospital (IRB No. H-2210-078-1368), which waived informed consent because of the retrospective design. The Institutional Data Review Board of Seoul National University Hospital approved public release after confirming adequate anonymisation (DRB No. BD-R-2022-11-02) [8]. This secondary analysis used only de-identified data accessed under the PhysioNet data-use agreement and involved no direct participant contact.

Clinical trial number: not applicable.

Consent for publication

Not applicable. The manuscript contains no identifiable individual-level information.

Availability of data and materials

INSPIRE version 1.4.2 is available to credentialed users through PhysioNet under its data-use agreement [9]. The analysis package contains study code, aggregate tables, and figures; patient-level derivatives should not be redistributed outside the governing agreement. Reproducible Python scripts used to construct the analytic cohort, audit the postoperative ventilation outcome, fit the models, compare oxygen metrics, and generate publication tables and figures are included in the accompanying analysis package.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SL and JY conceived and designed the study. SL, XC, RC, and ZY extracted, curated, and harmonised the data. SL and YH conducted the statistical analyses and generated the figures. SL drafted the manuscript. XC, RC, ZY, and YH critically revised the manuscript for important intellectual content. JY supervised the study and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Figures

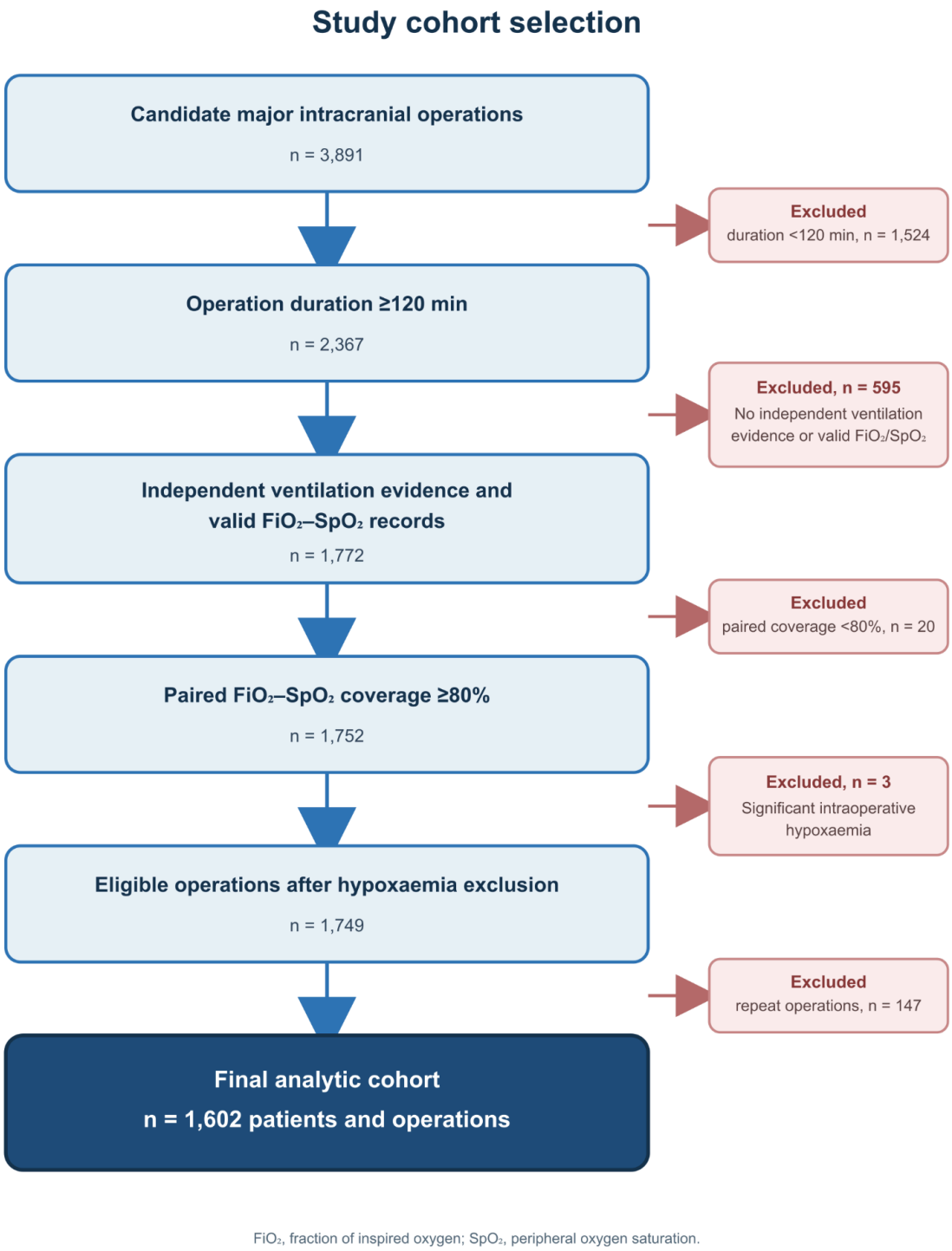

Figure 1

Study flow. The diagram shows sequential application of the minimum operation-duration criterion, independent intraoperative mechanical-ventilation evidence and valid FiO_2–SpO_2 records, paired-data coverage, hypoxaemia exclusion, and retention of the first eligible operation per patient.

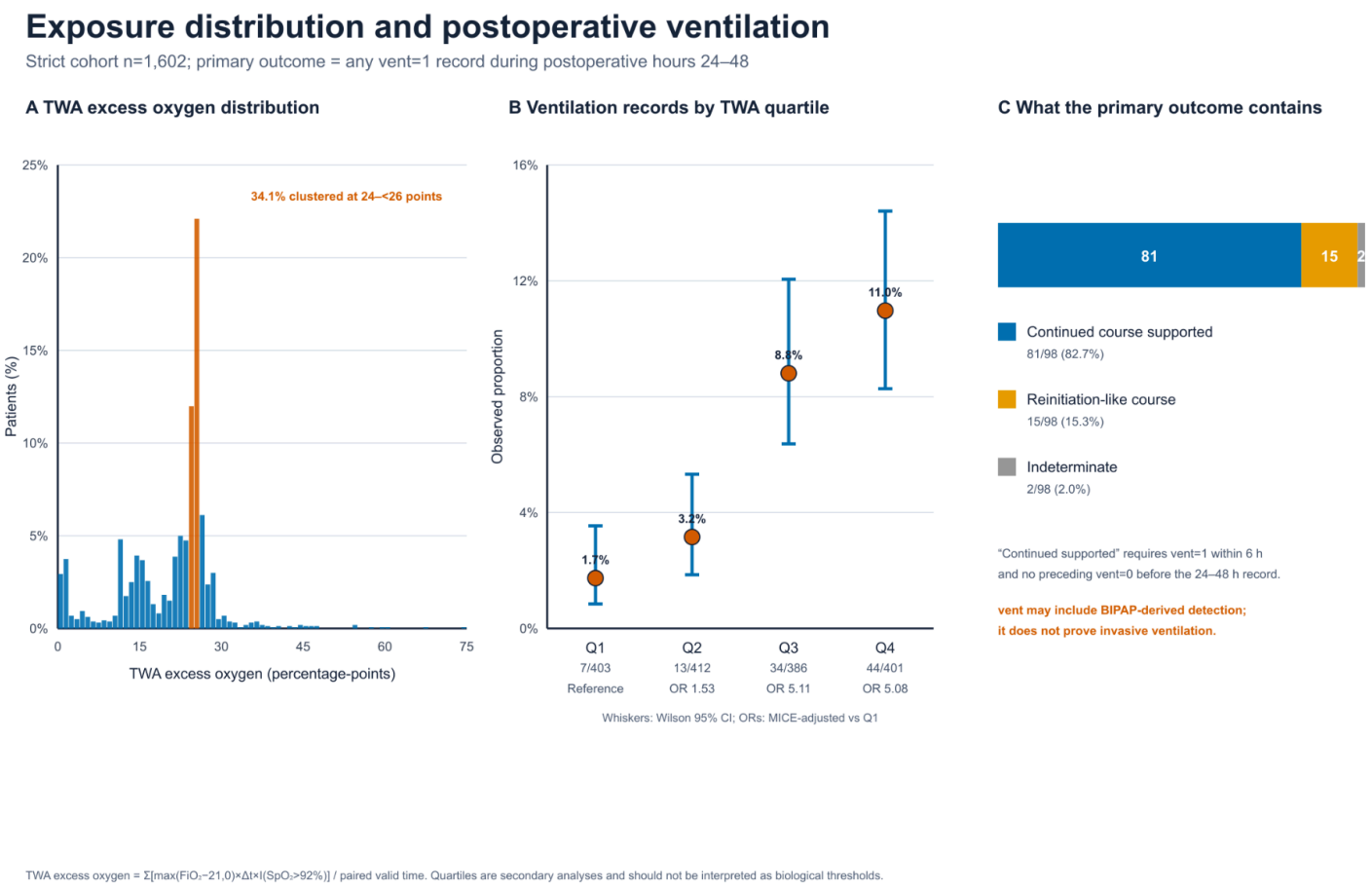

Figure 2

Exposure distribution, quartile outcome rates, and primary-outcome audit. Panel A shows the distribution of TWAEO; 34.1% of patients clustered at 24 to <26 percentage points. Panel B shows observed 24–48 h ventilation-record proportions with Wilson 95% CIs and MICE-adjusted quartile ORs. Quartiles are descriptive and do not define a biological threshold. Panel C partitions the 98 primary events into continued-supported, reinitiation/reintubation-like, and indeterminate temporal patterns. The ventilation field may include BIPAP-derived detection and does not prove invasive ventilation.

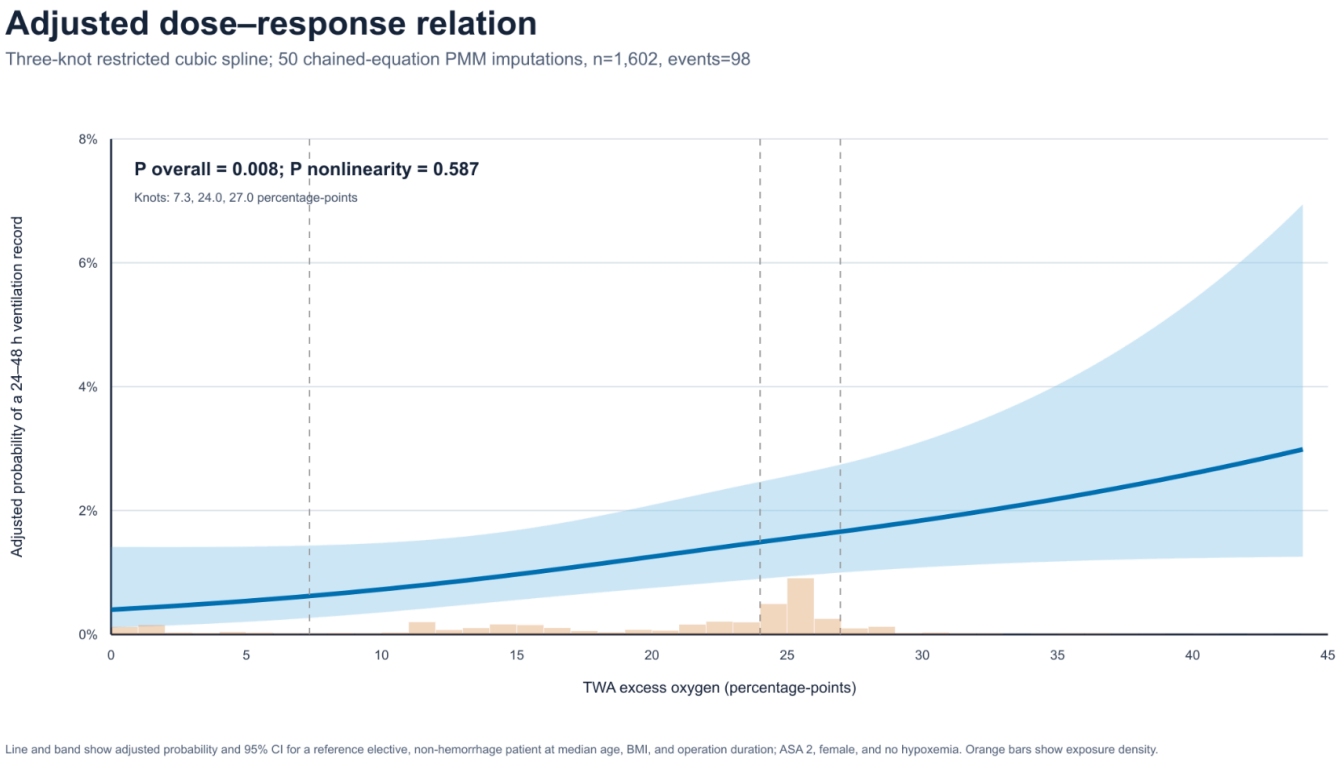

Figure 3

Adjusted dose–response relation between TWAEO and a 24–48 h ventilation record. The line and band show adjusted probability and 95% CI from a three-knot restricted cubic spline across 50 imputed datasets. Knots were placed at the 10th, 50th, and 90th exposure percentiles. Overall P=.008; non-linearity P=.587. Orange bars show the exposure density.

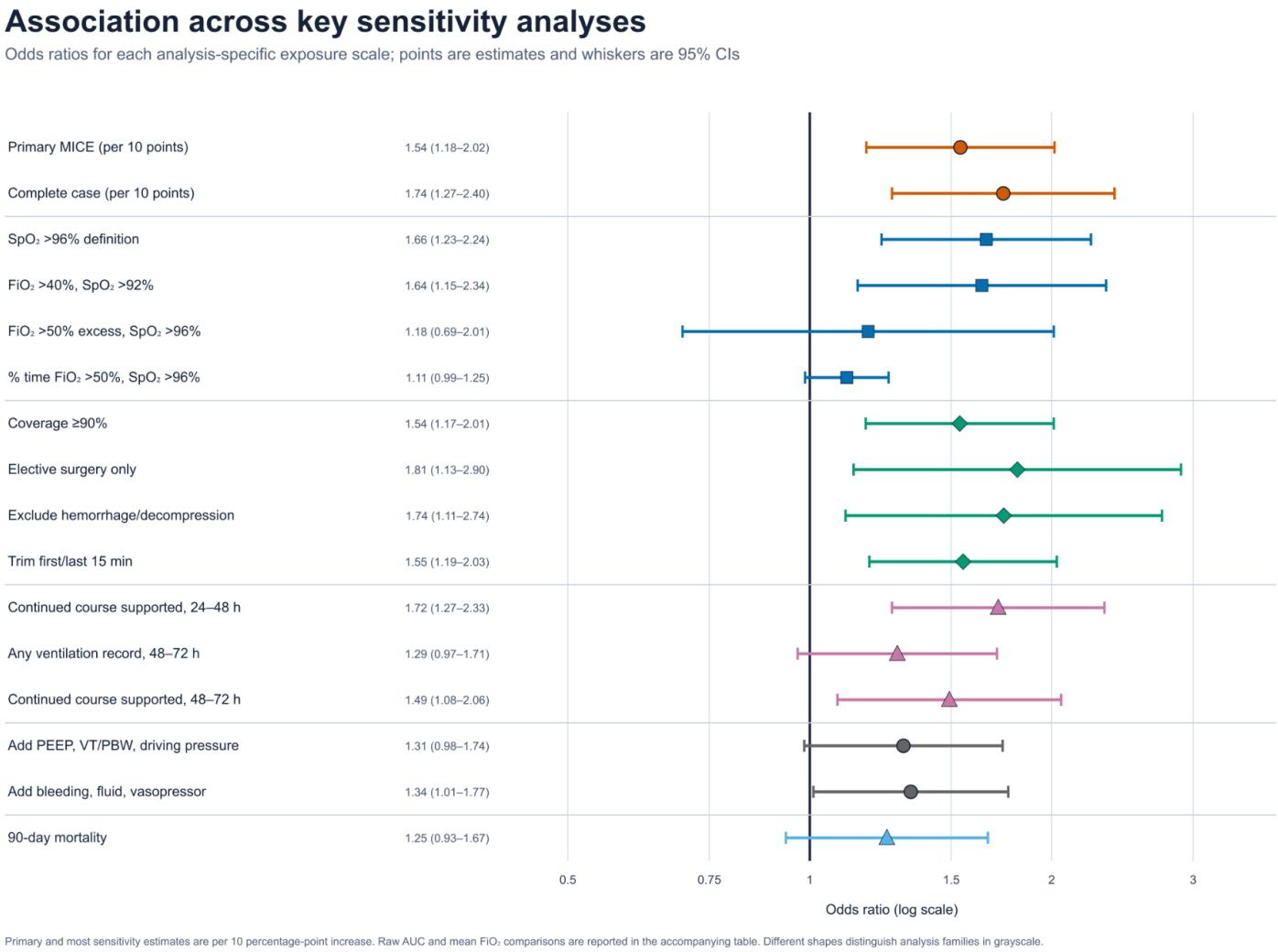

Figure 4

Key sensitivity analyses and secondary outcomes. Adjusted ORs and 95% CIs are shown for alternative exposure definitions, cohort restrictions, outcome audits, postoperative windows, additional covariate adjustment, and secondary outcomes. The attenuation in the ventilation-strategy model is a central interpretive limitation.

Supplementary Files

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- SupplementaryMaterialBMCAnesthesiology.docx