

Preoperative clear fluid fasting in patients undergoing nonemergency liver transplant: duration, hemodynamic and metabolic correlates. A prospective observational single-centre study

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Abstract

Background

Prolonged clear fluid fasting (CFF) is associated with adverse metabolic and hemodynamic effects, yet its real-world duration and clinical relevance in liver transplant (LT) candidates remain unknown. LT recipients are medically fragile and at high risk of periprocedural hemodynamic instability. Although guidelines permit clear liquids until 2 hours before anesthesia, actual CFF duration and its physiological consequences in LT have not been evaluated.

Methods

In this single-center prospective study, 99 adults undergoing nonemergency deceased-donor LT were enrolled. CFF duration was recorded and analyzed primarily as a continuous predictor using restricted cubic splines; median dichotomization (≤ 12 h vs. >12 h) was performed as a secondary, descriptive comparison. As a secondary, exploratory aim, four outcomes were assessed: post-induction hypotension and de novo hyperglycemia, hyperlactatemia and base deficit.

Results

Median preoperative CFF duration was 12.0 h (IQR 7.0 to 15.8); 3.0% of patients fasted within the recommended 2 hours. Modelled continuously, each additional hour of fasting was associated with 7.1% lower unadjusted odds of post-induction hypotension (OR 0.93 per hour, 95% CI 0.86 to 1.00), attenuating after adjustment (OR 0.93, 95% CI 0.85 to 1.01) and concordant for a composite of hypotension or vasopressor administration (OR 0.92, 95% CI 0.86 to 0.99); no estimate met the Bonferroni-adjusted threshold, and MAP trajectories did not differ. CFF duration showed no association with de novo hyperglycemia, hyperlactatemia or base deficit, including in a full-cohort continuous sensitivity analysis; these exploratory analyses were underpowered.

Conclusions

In this prospective study of LT recipient, preoperative CFF was substantially longer than recommended. CFF duration showed no significant association with metabolic derangements, though these exploratory analyses were underpowered. Its association with post-induction hypotension was inconclusive; residual confounding cannot be excluded. These findings do not provide evidence against the current 2-hour clear-fluid guideline and highlight a substantial gap between recommended and actual fasting practice; larger multicenter studies with standardized preoperative IV fluid protocols are needed to clarify its clinical consequences.

Trial registration:

NCT07288281, retrospectively registered on 2025-12-04

Introduction

Prolonged clear fluid fasting (CFF) has well-recognized adverse effects. It reduces patient wellbeing, increasing thirst, anxiety, and postoperative nausea and vomiting [1–3]. It can also contribute to preoperative hypovolemia and exacerbate arterial hypotension during anesthesia induction [4]. Prolonged preoperative fasting is also associated with adverse metabolic alterations, including increased postoperative insulin resistance, a heightened catabolic response, and greater blood glucose variability [5]. In 2011, the European Society of Anaesthesiology (ESA, now ESAIC) and, in 2017, the American Society of Anesthesiologists (ASA) stated in their preoperative fasting guidelines that clear liquids may be safely continued until 2 hours before anesthesia [6, 7]. Most recently, an international multidisciplinary consensus statement emphasized the need to improve patient care by minimizing periprocedural fasting times [8].

LT candidates are a particularly fragile and medically complex population. They have frequent metabolic derangements and a high propensity for periprocedural hemodynamic instability [9]. Two distinct pathways lead to LT: emergency transplantation for acute liver failure, and nonemergency transplantation for patients listed with chronic end-stage liver disease following structured preoperative evaluation [10]. Because deceased-donor organ availability is unpredictable, nonemergency candidates are called to the transplant center on short notice.

Current fasting guidelines are derived from general surgical populations and may not apply directly to patients with cirrhosis. Cirrhosis is associated with both delayed gastric emptying and reduced hepatic glycogen reserve, with an accelerated shift toward starvation metabolism within hours of fasting—competing considerations that argue against extrapolating general surgical guidelines to this population [11, 12].

Despite clear recommendations allowing clear fluids until 2 h before anesthesia and strong evidence supporting their safety in general surgical populations, no studies have specifically evaluated the actual duration or clinical impact of preoperative CFF in patients undergoing liver transplantation.

We hypothesized that, in real-world practice, preoperative CFF duration in patients undergoing nonemergency LT would substantially exceed the 2-hour guideline recommendation. The primary aim of this prospective observational study was to quantify the duration of preoperative CFF in this population. As a secondary, exploratory aim, we evaluated whether CFF duration was associated with post-induction hypotension and de novo metabolic derangements (hyperglycemia, hyperlactatemia, and base deficit).

1. Methods

1.1 Study design, settings and participants

This single center prospective observational cohort study was conducted as a collaborative project between the 2nd Department of Anesthesiology and Intensive Care and the Department of Transplant and Liver Surgery at the Medical University of Warsaw, a tertiary referral hospital in Poland. Ethical approval from the Bioethical Committee of the Medical University of Warsaw was obtained (KB/67/2025) and the study was registered at ClinicalTrials.gov (NCT07288281). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [13, 14].

Between June and October 2025, consecutive adult patients scheduled for nonemergency LT were prospectively enrolled. Based on the center's annual transplant volume and expected exclusions, the projected 6-month recruitment was estimated at ~ 100 patients, consistent with sample sizes in recent studies on similar perioperative endpoints [15]. The precision afforded by this administratively determined sample is quantified as design sensitivity: the realized design provided 80% power only for odds ratios at or below 0.31, and null findings are therefore interpreted as absence of evidence rather than evidence of absence.

The inclusion criteria for the study were: age ≥ 18 and planned nonemergency LT with a graft (whole or split) coming from a deceased donor irrespective of the indication for transplantation. Exclusion criteria were emergency LT, preoperative intubation, and inability to provide reliable information on the timing of last clear fluid intake due to severe hepatic encephalopathy or cognitive impairment.

1.2 Variables, data collection and measurements

All perioperative data were collected as a part of routine care using hospital electronic system and standardized case report form (CRF). At patients' arrival in the operating room, standardized intraoperative monitoring was instituted, including continuous ECG, pulse oximetry, and non-invasive blood pressure measurements at 5-minute intervals; arterial and central venous cannulation were subsequently performed following induction of anesthesia.

General anesthesia was induced with sufentanil (0.1–0.3 mcg/kg), propofol (1–2.5 mg/kg and infusion rate 30–40 mg/10 seconds), and succinylcholine or rocuronium, and maintained with sevoflurane. Drug doses and intraoperative fluid management were at the discretion of the attending anesthesiologist. Mean arterial pressure (MAP) was maintained above 65 mmHg using balanced crystalloids and vasopressors (ephedrine during immediate post-induction period or norepinephrine in further stage of surgery) as needed. Metabolic variables (glycemia, SBE, lactate concentration) were recorded after anesthesia induction and at the end of the anhepatic phase. The anhepatic phase was defined as the interval between removal of the native liver and reperfusion of the transplanted graft [16]. All laboratory measurements were obtained from arterial blood gas analysis (ABG) performed using point of care testing (POCT) devices as a part of routine LT care.

1.3 Primary outcome

The primary outcome was preoperative CFF duration, measured in hours and defined as the interval between the patient-reported last clear fluids intake and anesthesia induction. This variable was recorded prospectively in the operating room before induction of anesthesia. It was analyzed descriptively (median, interquartile range) as the primary endpoint of the study. In addition to this primary, descriptive characterization, it was also used as a continuous predictor in the secondary, exploratory analyses of post-induction hypotension and metabolic derangements (Section 1.4). The preferred analytic approach modeled CFF as a continuous predictor, using restricted cubic splines to characterize its association with outcomes without assuming linearity. Because dichotomizing a continuous exposure discards information and reduces statistical power [17], median dichotomization (Short CFF ≤ 12 h vs. Long CFF > 12 h) was retained only as a secondary, descriptive analysis to aid clinical interpretation. Alternative thresholds (6, 8, 10 h) were examined jointly, as a check on the stability of the effect direction across cut-points rather than to identify an optimal value; a data-driven optimized cut-point is not interpretable at face value.

1.4 Secondary, exploratory outcomes

Four secondary, exploratory outcomes were defined: post-induction hypotension; de novo hyperglycemia; de novo hyperlactatemia; de novo decrease SBE. These outcomes were pre-specified. The “de novo” construct restricted outcome assessment to patients with normal baseline values, thereby ensuring that only incident abnormalities attributable to the transplant procedure- rather than pre-existing pathology- were captured. Post-induction hypotension, defined- consistent with definitions used in prior perioperative hemodynamic studies [18]- as a MAP < 65 mmHg or a $> 30\%$ decrease from the first MAP measurement obtained in the operating room at any time point between 5 and 20 minutes after anesthesia induction (t_2-t_5); de novo hyperglycemia, defined as a rise in blood glucose from a normal baseline glycemia (≤ 100 mg/dL) to > 100 mg/dL during the anhepatic phase; de novo hyperlactatemia, defined as an increase from a normal baseline lactate (≤ 2.0 mmol/L) to > 2.0 mmol/L during the anhepatic phase; and de novo decrease SBE, defined as a decline from a normal baseline SBE (-2.5 to $+2.5$ mEq/L) to < -2.5 mEq/L during the anhepatic phase.

1.5 Additional exploratory outcome

MAP trajectory was assessed using five serial measurements recorded at baseline (pre-induction) and 5, 10, 15 and 20 minutes after induction of anesthesia. At each post-induction time point, hypotension was flagged when the mean arterial pressure fell below 65 mmHg or by more than 30% relative to the first reading.

1.6 Covariates and potential confounders

Pre-specified covariates included age, sex, body mass index (BMI, kg/m²), Model for End-Stage Liver Disease (MELD) 3.0 score, diabetes mellitus, primary transplant indication (grouped into 5 categories: alcohol-related liver disease (ALD), autoimmune/cholestatic disease, viral hepatitis, malignancy, and

other), anhepatic phase duration, and intraoperative fluid administration. Ephedrine administration during the post-induction period was recorded as a binary marker of vasopressor rescue.

1.7 Effect modifier

Pre-existing diabetes was specified a priori as an effect modifier of the CFF–hyperglycemia relationship, given the biologically plausible interaction between fasting-related glycogen depletion and the impaired suppression of hepatic gluconeogenesis in diabetic patients [19, 20].

1.8 Statistical Analysis

The statistical analysis plan, including the pre-specified outcome definitions, (Section 1.4) covariates and the Bonferroni-adjusted threshold below, was finalized before data access and was not modified after outcomes were examined. Following peer review, the framing of the study was revised: the description of CFF duration is now presented as the primary aim, and the four outcome analyses – originally designated co-primary in the registration (NCT07288281) – are presented as secondary and exploratory. No outcome definition, eligibility criterion or model specification was altered by this reframing. A two-sided $\alpha = 0.05$ was used as a descriptive reference threshold. Because the primary aim was to describe CFF duration (Section 1.3), the four outcome comparisons (Section 1.4) are secondary and exploratory. Unadjusted P values for these four comparisons are compared with a Bonferroni-adjusted threshold ($\alpha' = 0.05/4 = 0.0125$). The study was not powered to detect associations for these outcomes: significant results should not be read as confirmatory, and null results should not be read as evidence of no effect – both are hypothesis-generating. This applies equally to the additional exploratory analyses reported throughout (per-timepoint MAP comparisons, the spline non-linearity test, alternative dichotomization cut-points, the CFF $\times$ diabetes interaction test, stratum-specific odds ratios, AUROC comparisons, and effect-size estimates), none of which should be regarded as confirmatory.

1.8.1 Descriptive statistics and covariate balance

Continuous variables were summarized as mean $\pm$ SD or median (IQR). Between-group comparisons (Short CFF vs. Long CFF) used Wilcoxon rank-sum test or Pearson chi-squared/Fisher's tests. Covariate balance was assessed using the standardized mean difference (SMD) > 0.10 .

1.8.2 Logistic regression for secondary, exploratory binary outcomes

Binary outcomes were modelled by maximum-likelihood logistic regression. The number of estimated coefficients was governed by the events-per-variable (EPV) rule against the limiting (minority) class; no inferential model with EPV below 10 was fitted, and penalized estimation was not used. For post-induction hypotension the adjusted models retained an a priori parsimonious set (age and MELD; EPV 11.7); where the EPV constraint precluded adjustment, only descriptive statistics were reported. Discrimination was summarized by the apparent AUROC with a DeLong 95% CI, alongside the AUROC of a covariate-only model; the Hosmer-Lemeshow test was not reported, being uninformative at these event

counts. A full-cohort analysis of covariance modelled each anhepatic value continuously (adjusted for its baseline value, CFF, age, MELD and sex) to avoid the selection inherent in conditioning on a normal baseline.

1.8.3 Exploratory interaction analysis

The CFF group and diabetes mellitus (DM) interaction for the de novo hyperglycemia outcome was evaluated by using likelihood ratio comparison of models with and without the interaction term.

1.8.4 Exploratory MAP trajectory analysis

The intraoperative MAP trajectory was examined by two complementary approaches. First, MAP and the prevalence of post-induction hypotension were summarized at each time point by CFF group, the latter with Wilson 95% confidence intervals, giving a time-resolved account of hemodynamic exposure and hypotensive burden. Second, a linear mixed-effects model assessed trajectory differences using time, CFF group and their interactions.

1.8.5 Exploratory sensitivity analyses

CFF was modeled as a continuous predictor using restricted cubic splines as the preferred analytic approach for characterizing this secondary, exploratory outcome association, allowing for non-linearity in the dose–response relationship. Three further sensitivity analyses were performed to complement this continuous model and evaluate robustness: – median dichotomization of CFF (Short vs. Long CFF) as a descriptive, clinically interpretable comparison; – joint evaluation of alternative dichotomization thresholds (6, 8, 10 h) to assess the stability of the effect direction across cut-points, without designating any single threshold (including 8 h) as an optimal or independently interpretable value; – adjustment for ephedrine use.

1.8.6 Effect size estimation

Standardized effect sizes (Cohen's d, rank-biserial r, phi, Cramér's V) were calculated with 95% CIs.

1.8.7 Missing data

The main analyses were conducted on available cases. Missingness in the de novo outcomes were structural (patients with abnormal baseline values are inherently ineligible) and < 5%; imputation was not required.

1.8.8 Software and reproducibility

All analyses were performed in R version 4.6.1 with a fixed random seed (20260817). The complete analysis pipeline – import, validation, derivation of the de novo outcomes from raw laboratory values, modelling, and generation of every table and figure – is deterministic and executable end-to-end by a single script. The R analysis code, codebook and data dictionary are available from the corresponding author and in Supplemental Digital Content (see Availability of data and materials).

2. Results

2.1 Participants, data completeness and CFF distribution

Between 1 June and 31 October 2025, 118 patients were assessed for eligibility, of whom 100 were enrolled, as shown in Fig. 1 (Fig. 1 Flow diagram of patient recruitment and study inclusion); recruitment ended once the predefined sample size was reached, the principal reasons for exclusion being preoperative intubation and severe hepatic encephalopathy. After exclusion of 1 participant with missing data, the final analytic cohort comprised 99 adults (62 male, 37 females; mean age 51.5 ± 12.8 years). The most prevalent transplant indications were alcohol-related liver disease (29.3%), autoimmune or cholestatic disease (28.3%) and viral hepatitis (13.1%); the median MELD score was 13 (IQR 11 to 19). One patient experienced aspiration during anesthesia induction. Data completeness was excellent across demographic, hemodynamic and treatment variables. Baseline laboratory missingness was limited to glucose (2.0%), lactate (3.0%) and SBE (4.0%). The de novo metabolic outcomes, derived directly from the raw laboratory values, were assessed only in patients with a normal baseline value and an available anhepatic measurement, yielding evaluable cohorts of 40 (hyperglycemia), 71 (hyperlactatemia) and 47 (base deficit) patients. An anhepatic-phase measurement was unavailable in 24 to 25 patients (approximately 25%), a source of reduced subsets distinct from ineligibility due to an abnormal baseline; in addition, 3 patients had severe intraoperative hemorrhage and 2 received intraoperative hemodialysis. A participant-flow account for each endpoint is provided in Table S1. No imputation was undertaken.

2.2 Duration of preoperative CFF

Median CFF duration was 12.0 h (IQR 7.0–15.8 h; bootstrap 95% CI 9.0–13.0 h), ranging from 0 to 32 h across the cohort. Three of 99 patients (3.0%; 95% CI 1.0 to 8.5) had fasted within the guideline-recommended 2 hours, whereas 79.8% had fasted longer than 6 hours, 42.4% longer than 12 hours, 22.2% longer than 16 hours and 2.0% longer than 24 hours (Table 1, Fig. 2 Distribution of preoperative clear fluid fasting duration in 99 liver transplant recipients). For the secondary analyses below, CFF was additionally dichotomized at the sample median, assigning 57 patients (57.6%) to Short CFF and 42 patients (42.4%) to Long CFF (Fig. 2). The Spearman correlation matrix (Fig. S1 Spearman rank correlations among baseline and intraoperative variables) confirmed that CFF was weakly correlated with other baseline variables (all absolute $\rho < 0.22$), supporting its use as a largely independent predictor.

Table 1
Duration of preoperative clear fluid fasting and concordance with the 2-hour guideline

Fasting category	Patients, n	%	95% CI, %
Within 2-h guideline (≤ 2 h)	3	3.0	1.0–8.5
> 6 h	79	79.8	70.8–86.5
> 12 h	42	42.4	33.2–52.3
> 16 h	22	22.2	15.2–31.4
> 24 h	2	2.0	0.6–7.1
Note. Median CFF duration 12.0 h (IQR 7.0–15.8; bootstrap 95% CI 9.0–13.0); range 0–32 h. Proportions with Wilson 95% CI; n = 99. CFF, clear fluid fasting.			

2.3 Descriptive data

Baseline characteristics stratified by CFF group are presented in Table 2. The 2 groups were generally well-matched, with no statistically significant differences detected at $\alpha = 0.05$. However, inspection of SMDs revealed several covariates exceeding the pre-specified 0.10 threshold for clinically meaningful imbalance, warranting adjustment in multivariable models.

Table 2
Baseline characteristics stratified by clear fluid fasting group

Characteristic	Short CFF (n = 57)	Long CFF (n = 42)	SMD
Demographics			
Age, years	52 [44–62]	52 [38–62]	0.153
Female sex, n (%)	21 (36.8)	16 (38.1)	0.026
Body mass index, kg/m ²	25.0 [23.0–29.0]	25.0 [22.0–27.0]	0.052
Liver disease severity and etiology			
MELD 3.0 score	13 [10–17]	15 [12–20]	0.254
Diabetes mellitus, n (%)	18 (31.6)	11 (26.2)	0.119
Primary indication, n (%)			0.378
Alcohol-related liver disease	19 (33.3)	10 (23.8)	
Autoimmune or cholestatic	15 (26.3)	13 (31.0)	
Viral hepatitis	7 (12.3)	6 (14.3)	
Malignancy	8 (14.0)	3 (7.1)	
Other	8 (14.0)	10 (23.8)	
Preoperative exposure			
CFF duration, h	8.0 [5.5–10.0]	16.5 [14.6–18.5]	2.789
Baseline hemodynamics			
Mean arterial pressure, mmHg	98 [88–111]	92 [82–102]	0.324
Heart rate, beats/min	77 [68–88]	78 [66–84]	0.169
Baseline metabolic status			
Glucose, mg/dL	103 [92–111]	99 [91–117]	0.162
Lactate, mmol/L	1.1 [0.9–1.5]	1.1 [0.9–1.4]	0.059
Standard base excess, mEq/L	–1.6 [– 2.9 to – 0.1]	–0.8 [– 2.4 to 0.1]	0.161
Intraoperative management			
Crystalloids, mL	3000 [2500–3500]	3500 [2962–3875]	0.225
Colloids, n (%)	15 (26.3)	16 (38.1)	0.254
<i>Note.</i> Data are median [IQR] or n (%). Groups defined by the sample median: Short CFF ≤ 12 h, Long CFF > 12 h. SMD > 0.10 indicates a potential imbalance. CFF, clear fluid fasting; MELD, Model for End-Stage Liver Disease; SMD, standardized mean difference.			

Characteristic	Short CFF (n = 57)	Long CFF (n = 42)	SMD
Demographics			
Blood products, n (%)	21 (36.8)	20 (47.6)	0.219
Ephedrine rescue at induction, n (%)	14 (24.6)	8 (19.0)	0.134
Anhepatic duration, min	112 [84–134]	106 [90–128]	0.085
<i>Note.</i> Data are median [IQR] or n (%). Groups defined by the sample median: Short CFF $\leq$ 12 h, Long CFF $>$ 12 h. SMD $>$ 0.10 indicates a potential imbalance. CFF, clear fluid fasting; MELD, Model for End-Stage Liver Disease; SMD, standardized mean difference.			

Baseline MAP was lower in the Long CFF group (median 91.5 vs. 98.0 mmHg, $P = .071$, SMD = 0.324). The Long CFF group trended toward higher MELD scores (median 15.0 vs. 13.0, $P = .072$, SMD = 0.254) and greater intraoperative crystalloid administration (median 3500 vs. 3000 mL, $P = .064$, SMD = 0.225).

Between-group effect sizes, computed as rank-biserial correlations for continuous variables and phi coefficients for binary variables (SDC), confirmed the pattern observed in the SMD analysis. Baseline MAP ($r = 0.213$, 95% CI: -0.015 to 0.420) and MELD score ($r = -0.212$, 95% CI: -0.419 to 0.016) exhibited small-to medium effect sizes. All phi coefficients for binary covariates were negligible ($\phi \leq 0.08$), affirming adequate balance for categorical variables, as summarized in the standardized-difference plot (Fig. S2 Baseline covariate balance between clear fluid fasting groups).

The distribution of primary transplant indications was comparable across groups (χ^2 test $P = .507$, SMD = 0.378; Cramér's $V = 0.000$). Age, BMI, sex, DM prevalence, and baseline metabolic markers (glucose, lactate, SBE) were well-balanced (all SMD < 0.17). Based on these findings, the a priori covariate set (age, sex, BMI, MELD) was retained for all adjusted models, with the number of covariates further restricted by the EPV rule where necessary.

2.4 Post-induction hypotension

Hypotension after induction of anesthesia occurred in 64 of 99 patients (64.6%). Modelled continuously, each additional hour of fasting was associated with 7.1% lower odds of hypotension (unadjusted OR 0.93 per hour, 95% CI 0.86 to 1.00, $P = .05$); after a priori adjustment for age and MELD (EPV 11.7, maximum VIF 1.13, Nagelkerke R-squared 0.302) the estimate was essentially unchanged and non-significant (OR 0.93, 95% CI 0.85 to 1.01, $P = .11$).

The secondary median-dichotomized comparison was directionally consistent but non-significant (unadjusted OR 0.47, 95% CI 0.20 to 1.09; adjusted OR 0.42, 95% CI 0.16 to 1.10). The apparent AUROC of the adjusted model was 0.792 (95% CI 0.698 to 0.887); a covariate-only model without CFF already reached 0.780, so CFF added negligibly to discrimination and the model should not be described as clinically discriminating. No estimate met the Bonferroni-adjusted threshold (Table 3, Fig. 3 Odds ratios for post-induction hypotension across model specifications).

Table 3
Association between clear fluid fasting duration and post-induction hypotension

Model	Odds ratio		Model diagnostics				Discrimination	
	OR	95% CI	P	EPV	VIF	R ²	AUROC	95% CI
Per 1-h increase, unadjusted	0.93	0.86–1.00	.05	35.0	–	0.057	0.620	0.508–0.732
Per 1-h increase, adjusted	0.93	0.85–1.01	.11	11.7	1.13	0.302	0.792	0.698–0.887
Long vs Short, unadjusted	0.47	0.20–1.09	.08	35.0	–	0.042	0.592	0.489–0.694
Long vs Short, adjusted	0.42	0.16–1.10	.08	11.7	1.13	0.306	0.802	0.708–0.896
<i>Note.</i> Maximum-likelihood logistic regression; adjusted models include age and MELD. AUROC is apparent, with DeLong 95% CI; the covariate-only model (without CFF) had AUROC 0.780. Bonferroni-adjusted threshold P = .0125. EPV, events per variable; VIF, variance inflation factor; R², Nagelkerke R²; AUROC, area under the receiver operating characteristic curve; CFF, clear fluid fasting.								

Alternative dichotomization thresholds (6, 8 and 10 h) were examined jointly (Table S2); estimates were directionally consistent, with only the 8-hour threshold reaching nominal significance (OR 0.37, 95% CI 0.13 to 0.92), a data-driven result not interpretable as a meaningful cut-point. When the endpoint was broadened to a composite of post-induction hypotension or ephedrine administration in post-induction period (66 of 99 patients, 66.7%), the estimate was concordant with the primary analysis (OR 0.92 per hour, 95% CI 0.86 to 0.99, P = .038; Table S3) and, like it, did not meet the Bonferroni-adjusted threshold.

2.5 Exploratory post-induction MAP trajectory

The serial MAP trajectory from baseline through 20 minutes post-induction is depicted in Fig. 4 (Fig. 4 Mean arterial pressure trajectory after induction of anesthesia by clear fluid fasting group) with summary statistics and formal testing presented in Table 4. Both CFF groups demonstrated a sharp decline in MAP between baseline and 5 minutes (Short CFF: 98.3 → 77.3 mmHg, Δ = -21.0; Long CFF: 93.5 → 76.0 mmHg, Δ = -17.5), followed by relative stabilization between 10 and 20 minutes.

Table 4

Post-induction mean arterial pressure and post-induction hypotension over time, by clear fluid fasting group

Time, min	MAP, mmHg (mean $\pm$ SD)		Post-induction hypotension, n/N (%)	
	Short CFF	Long CFF	Short CFF	Long CFF
0 (baseline)	98 $\pm$ 15	94 $\pm$ 15	–	–
5	77 $\pm$ 16	76 $\pm$ 12	17/57 (30)	12/42 (29)
10	76 $\pm$ 14	74 $\pm$ 12	21/57 (37)	14/42 (33)
15	73 $\pm$ 14	74 $\pm$ 10	27/57 (47)	15/42 (36)
20	73 $\pm$ 12	71 $\pm$ 10	25/57 (44)	17/42 (40)
<i>Note.</i> Group summaries at each post-induction time point. Post-induction hypotension is a mean arterial pressure below 65 mmHg or a decrease exceeding 30% from the first reading; Wilson 95% CIs are shown in Figure S3, and hypotension is undefined at baseline (–). Linear mixed-effects model (MAP $\sim$ time $\times$ CFF group + [1 patient]): time-by-group interaction $P = .45$; CFF group main effect (additive model) Long minus Short = -1.8 mmHg ($P = .36$). Per-timepoint between-group tests are not reported. MAP, mean arterial pressure; SD, standard deviation; CFF, clear fluid fasting.				

The Short CFF group had a numerically higher baseline MAP (98.3 vs 93.5 mmHg), and this relative separation persisted across subsequent time points before the groups converged by 15 to 20 minutes. The linear mixed-effects model (MAP $\sim$ time $\times$ CFF group + [1 | patient]) showed no time-by-group interaction (likelihood ratio test $P = .45$) and no group main effect (Long minus Short = -1.8 mmHg, $P = .36$), indicating that the shape of the MAP trajectory did not differ between groups. Per-timepoint tests were not performed, to avoid unnecessary multiplicity.

MAP fell sharply within the first 5 minutes after induction and then plateaued in both groups (Table 4). The prevalence of post-induction hypotension increased over the first 15 minutes and was modestly higher in the Short CFF group between 10 and 20 minutes (for example, 47% versus 36% at 15 minutes), although the Wilson confidence intervals overlapped at every time point (Fig. S3 Post-induction hypotension dynamics by clear fluid fasting group). Individual trajectories disclosed occasional profound episodes, the lowest recorded MAP being 37 mmHg.

2.6 De Novo metabolic derangements

2.6.1 De novo hyperglycemia

Among 40 patients eligible under the corrected definition (baseline glucose ≤ 100 mg/dL with an available anhepatic measurement), 28 (70.0%; 95% CI 54.6 to 81.9) developed de novo hyperglycemia during the anhepatic phase. CFF duration was not associated with this outcome (OR 0.97 per hour, 95% CI 0.87 to 1.08, $P = .55$; Long vs Short OR 0.71, 95% CI 0.17 to 2.78). In the full-cohort ANCOVA the adjusted change in anhepatic glucose was -0.30 mg/dL per hour ($P = .64$), confirming no association (Table 5, Fig. 5 Clear fluid fasting and intraoperative metabolic outcomes).

Table 5
De novo metabolic outcomes and their association with clear fluid fasting duration

Outcome	Patients, n	Events, n (%)	Per 1-h increase			Long vs Short CFF		
			OR	95% CI	P	OR	95% CI	P
De novo hyperglycemia	40	28 (70.0)	0.97	0.87–1.08	.55	0.71	0.17–2.78	.63
De novo hyperlactatemia	71	68 (95.8)	NC	–	–	NC	–	–
De novo base deficit	47	27 (57.4)	1.08	0.97–1.22	.18	3.39	1.03–12.25	.05

Note. De novo: normal baseline value and an available anhepatic measurement; event = anhepatic value beyond threshold (glucose > 100 mg/dL; lactate > 2.0 mmol/L; standard base excess < – 2.5 mEq/L). Event proportions have Wilson 95% CI (hyperglycemia 54.6–81.9; hyperlactatemia 88.3–98.6; base deficit 43.3–70.5). Unadjusted maximum-likelihood logistic regression. NC, not computed (hyperlactatemia has 3 non-events; analysed continuously in Table 6). OR, odds ratio; CFF, clear fluid fasting.

2.6.2 De novo hyperlactatemia

De novo hyperlactatemia (baseline lactate $\leq$ 2.0 mmol/L rising to > 2.0 mmol/L in the anhepatic phase) occurred in 68 of 71 eligible patients (95.8%; 95% CI 88.3 to 98.6). With only 3 non-events this near-ceiling outcome was not modelled (EPV 3); instead, the full-cohort ANCOVA analyzed anhepatic lactate continuously and showed no association with CFF (adjusted geometric ratio 1.001 per hour, $P = .92$).

2.6.3 De novo base deficit

Among 47 eligible patients, 27 (57.4%; 95% CI 43.3 to 70.5) developed de novo base deficit (SBE < – 2.5 mEq/L) during the anhepatic phase (Table 5). The continuous association with CFF was null (OR 1.08 per hour, 95% CI 0.97 to 1.22, $P = .18$; age-adjusted identical, EPV 10). The secondary median-dichotomized comparison was nominally significant but imprecise and in the harmful direction (OR 3.39, 95% CI 1.03 to 12.25, $P = .05$); it did not persist in the full-cohort ANCOVA (adjusted change – 0.04 mEq/L per hour, $P = .37$) and is most parsimoniously a chance finding among multiple exploratory comparisons.

2.7 Exploratory effect modification by diabetes

The pre-specified CFF-by-diabetes interaction for de novo hyperglycemia could not be evaluated: only 10 eligible patients were diabetic (8 events, 2 non-events), precluding any stratum-specific model that respects the EPV rule. Observed stratum proportions are reported descriptively with Wilson confidence intervals and carry no inferential weight; no odds ratio or interaction test is reported. Table S4 reports these stratum-specific proportions with Wilson 95% confidence intervals. Among non-diabetic patients, the de novo hyperglycemia rate was comparable across CFF groups (~ 35–40%). Among diabetic patients, the Long CFF group showed a numerically higher rate, but this comparison rests on very few events and is exploratory only; it should not be read as evidence of effect modification by diabetes.

2.8 Exploratory, non-multiplicity-adjusted robustness and sensitivity of the hypotension finding

Given that hypotension was the only outcome showing a potentially meaningful signal, a suite of pre-specified sensitivity analyses was conducted to evaluate its robustness across analytic choices. These are synthesized below and presented in detail in Table 3 and Tables S2–S3.

2.8.1 Continuous modelling and dose–response shape

When CFF was modelled as a continuous predictor, the estimated OR per 1-hour increase was 0.93 (95% CI 0.86 to 1.00, $p = .047$), reaching nominal significance. This did not meet the pre-specified Bonferroni-adjusted threshold ($\alpha' = 0.0125$) for these secondary, exploratory comparisons. This translates to a 7.1% reduction in hypotension odds per additional hour of fasting. The restricted cubic spline model (Fig. 6 Dose–response relationship between continuous clear fluid fasting duration and post-induction hypotension) demonstrated a monotonically decreasing dose–response curve, with the steepest decline between approximately 4 and 14 hours. The non-linearity test was not significant, supporting the adequacy of a linear log-odds specification for this predictor.

2.8.2 Alternative dichotomization thresholds

The stability of the CFF–hypotension association across the choice of cut-point was evaluated jointly at 6, 8, 10, and 12 hours (Table 3, Table S2); this comparison was intended to assess whether the direction of effect was robust to the categorization threshold, not to identify or validate an optimal cut-point. All four thresholds yielded directionally consistent odds ratios below 1 (6 h: OR = 0.39; 8 h: OR = 0.37; 10 h: OR = 0.46; 12 h: OR = 0.47), with the 8-hour threshold showing a numerically larger, nominally significant estimate (95% CI: 0.14–0.96, $P = .041$). Because this threshold was one of several examined rather than a pre-specified single cut-point, and because searching across multiple thresholds inflates the chance of a nominally significant result at any one of them, this p-value should not be interpreted as evidence that 8 hours is a meaningful or generalizable clinical threshold. None of these threshold-specific estimates met the pre-specified Bonferroni-adjusted threshold ($\alpha' = 0.0125$); the consistent direction across thresholds should be read only as a sensitivity check, not as independent confirmation of an effect.

Discussion

This single-center prospective observational study was designed primarily to describe the duration of preoperative CFF in patients undergoing nonemergency LT, with a secondary aim of examining its association with post-induction hypotension and intraoperative metabolic derangements. In our cohort, the median preoperative CFF duration was 12 hours. We found no consistent association between CFF duration and post-induction hypotension, and no association with metabolic derangements.

Our findings should be considered against two strands of prior evidence. First, contemporary reviews of pre-transplant optimization emphasize a growing range of pharmacologic, nutritional, and behavioral

interventions used to prepare LT candidates for surgery, yet preoperative fasting duration itself has received little attention as a modifiable target within this framework [21]. Our finding that CFF durations substantially exceed guideline recommendations suggests this gap warrants closer attention. Second, prolonged preoperative fasting has been linked to unfavorable outcomes in other high-risk surgical populations: among critically ill patients undergoing gastrointestinal surgery, prolonged fasting was associated with longer mechanical ventilation, more postoperative myocardial injury, and higher reoperation rates than regular fasting times [22]. Our study did not replicate this pattern for post-induction hypotension or metabolic derangements; however, our exploratory, single-center analyses were considerably smaller and assessed different outcomes and were likely underpowered to detect effects of comparable magnitude.

Recent studies indicate that excessive preoperative CFF remains a persistent problem across Europe [23]. Patients awaiting LT are especially vulnerable to prolonged fasting because of transplant logistics — shifting organ arrival times, graft transport delays, and additional graft assessment — as well as inconsistent communication and patient-related uncertainty about surgical timing. Because this gap reflects logistics and communication rather than clinical necessity, closing it will likely require system-level interventions, such as protocolized communication between coordinators, surgical teams, and patients, rather than changes to anesthetic management.

Prolonged CFF may be associated with hypovolemia and an increased incidence of hypotension during anesthesia induction, and shorter CFF durations (≤ 2 h) have been shown to improve hemodynamic stability [24]. However, the magnitude of the post-induction MAP decline did not differ significantly between the groups in our cohort (Long vs Short CFF, $\Delta = -21.0$ vs -17.5 mmHg, respectively). This runs counter to the prevailing hypothesis that prolonged fasting induces volume depletion and thereby increases hemodynamic vulnerability. In the continuous analysis, longer CFF duration was associated with modestly lower odds of hypotension (OR 0.93 per hour, 95% CI 0.86 to 1.00). The dichotomized comparison (Long vs Short CFF), however, yielded a substantially wider, null-inclusive confidence interval (adjusted OR 0.42, 95% CI 0.16 to 1.10, $P = .08$). None of these estimates met the pre-specified Bonferroni-adjusted threshold ($\alpha' = .0125$); by this criterion, the hypotension analyses are formally negative. The confidence intervals are compatible with both a modest protective association and no association, and the point estimate should not be read as evidence of a hemodynamically protective effect of prolonged fasting. The most plausible explanation, should any real association exist, is residual confounding by indication. Preoperative intravenous fluid administration was not standardized at our institution, and patients with longer CFF also showed a sicker profile (higher MELD, lower baseline MAP) and greater intraoperative crystalloid use. This pattern suggests more clinician-directed fluid support overall, potentially including before arrival to the operating room. Such unmeasured preoperative hydration, rather than CFF duration itself, may account for the observed pattern. A composite endpoint that additionally counted ephedrine use at post-induction period — was concordant with the primary analysis (OR 0.92 per hour, 95% CI 0.86 to 0.99; Table S3), indicating that the signal is not an artifact of rescue treatment.

Clinically, this finding should not be used to justify prolonging preoperative CFF, nor does it weaken the rationale for adhering to the 2-hour clear-fluid guideline; it should instead be regarded as hypothesis-generating, warranting confirmation in studies with standardized perioperative fluid management.

Similarly, we found no statistically significant association between CFF duration and de novo hyperglycemia, hyperlactatemia, or base deficit. These exploratory analyses were based on small subgroups (40–71 patients) with correspondingly wide confidence intervals – particularly for hyperlactatemia (aOR = 0.54, 95% CI: 0.06–4.05) – and should therefore be interpreted as inconclusive rather than as evidence that CFF duration has no metabolic effect. The metabolic alterations observed during the anhepatic phase more likely reflect the intrinsic constraints of this period, such as impaired lactate clearance and altered acid–base homeostasis, though our data cannot rule out a modest, undetected contribution from preoperative fasting.

One patient aspirated during anesthesia induction. This patient had fasted for 7 hours, well beyond the 2-hour clear-fluid threshold. The event therefore does not challenge the safety of the 2-hour guideline itself. The patient also had large-volume ascites. Ascites is a recognized, independent risk factor for aspiration: it raises intra-abdominal pressure and can delay gastric emptying. This single event is more plausibly explained by ascites than by fasting duration. It highlights that aspiration risk in LT candidates depends on more than CFF duration alone. Individualized precautions – such as rapid sequence induction and intubation or preoperative gastric ultrasound – may be warranted in patients with significant ascites, irrespective of fasting time.

This study has several limitations. First, we did not record patient-reported well-being outcomes such as thirst or anxiety, which would have strengthened the clinical relevance of our findings. Second, post-induction hypotension was assessed using non-invasive blood pressure monitoring rather than continuous invasive arterial monitoring, which may have reduced sensitivity to rapid hemodynamic changes in the immediate post-induction period. Third, preoperative intravenous fluid administration before arrival to the operating room was not recorded or standardized, precluding direct adjustment for this plausible confounder; a repeat of this study would prospectively capture preoperative fluid volumes and timing. Fourth, the de novo outcome construct conditions on a normal baseline value and therefore entails selection; the full-cohort analysis of covariance (Table 6), which models each anhepatic value continuously without baseline conditioning, addresses this and yielded concordantly null results. Fifth, this was a single-center study with a modest sample size: the design provided 80% power only for odds ratios at or below 0.31 (Table 7, Fig. 7 Design sensitivity of the post-induction hypotension analysis), the metabolic outcomes exhibited near-ceiling or floor event rates, and the pre-specified CFF × diabetes interaction could not be evaluated because only 10 of the 29 diabetic patients in the cohort were eligible for the de novo hyperglycemia analysis (8 events); a multicenter design – approximately 273 patients per group to detect an odds ratio of 0.60, or 145 per group for 0.50 – would be needed to confirm our findings and improve precision.

Table 6
Full-cohort sensitivity analysis (analysis of covariance) of anhepatic metabolic values

Anhepatic outcome	n	Per 1-h increase			Long vs Short CFF		
		Effect	95% CI	P	Effect	95% CI	P
Glucose, mg/dL	75	-0.30	-1.56 to 0.96	.64	-1.45	-16.19 to 13.29	.85
Lactate, ratio	74	1.001	0.987 to 1.015	.92	0.971	0.823 to 1.146	.72
Standard base excess, mEq/L	73	-0.04	-0.13 to 0.05	.37	-0.32	-1.39 to 0.75	.55
Note. Linear regression of each anhepatic value on its baseline value, CFF, age, MELD and sex. Effects are adjusted mean differences (per 1-h CFF, or Long vs Short); lactate is modelled on the natural-log scale, so its effect is a multiplicative ratio. ANCOVA, analysis of covariance; CFF, clear fluid fasting.							

Table 7
Design sensitivity, required sample size, and E-value robustness

Quantity	Value
Precision of the observed design	
Minimal detectable OR at 80% power	0.31
Power at the observed adjusted OR (0.42)	54%
Required sample size, future study	
Per group to detect OR 0.60	273
Per group to detect OR 0.50	145
E-value (unmeasured confounding)	
Hypotension, point estimate (OR 0.42)	2.46
Hypotension, confidence limit nearest null	1.00
Base deficit, point estimate (OR 3.39)	3.09
Base deficit, confidence limit nearest null	1.14
Note. Design sensitivity for the observed hypotension analysis (57 vs 42 patients; reference rate 71.9%); two-sided $\alpha = .05$. Future sample size assumes 1:1 allocation and 80% power. E-value on the risk-ratio scale. OR, odds ratio.	

Finally, the four secondary outcome comparisons and the numerous supporting analyses were exploratory and not adjusted for multiplicity; findings should therefore be interpreted as hypothesis-generating rather than confirmatory. These limitations notwithstanding, the study's prospective design,

pre-specified outcome definitions, and STROBE-concordant reporting support the reliability of the reported associations as hypothesis-generating findings.

In conclusion, patients undergoing nonemergency LT experience preoperative CFF durations well beyond current guideline recommendations, without clear evidence that this excess fasting affects post-induction hemodynamics or intraoperative metabolic stability. Given the observational design and the exploratory nature of our outcome analyses, these findings should not be taken as reassurance to prolong fasting, nor as grounds to abandon the 2-hour clear-fluid guideline. Reducing preoperative CFF towards recommended durations remains a reasonable target to improve patient comfort, and larger multicenter studies with standardized perioperative fluid protocols are needed to clarify its hemodynamic and metabolic consequences in this high-risk population.

Abbreviations

ABG

Arterial blood gas

ALD

Alcohol-related liver disease

ANCOVA

Analysis of covariance

aOR

Adjusted odds ratio

ASA

American Society of Anesthesiologists

AUC

Area under the curve

AUROC

Area under the receiver operating characteristic curve

BMI

Body mass index

CFF

Clear fluid fasting

CI

Confidence interval

CRF

Case report form

DM

Diabetes mellitus

ECG

Electrocardiogram

EPV

Events per variable
ESAIC
European Society of Anaesthesiology and Intensive Care
IQR
Interquartile range
IV
Intravenous
LRT
Likelihood ratio test
LT
Liver transplant / liver transplantation
MAP
Mean arterial pressure
MELD
Model for End-Stage Liver Disease
OR
Odds ratio
POCT
Point-of-care testing
RCS
Restricted cubic spline
SBE
Standard base excess
SD
Standard deviation
SMD
Standardized mean difference
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
VIF
Variance inflation factor

Declarations

Ethics approval and consent to participate

This study was approved by the Bioethical Committee of the Medical University of Warsaw (Approval No. KB/67/2025) and the study was registered at ClinicalTrials.gov (NCT07288281). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

PD: conceptualization, methodology, investigation, writing- original draft; WK: investigation, project administration; PA: resources, supervision; MG: resources; FB: writing- reviewing and editing, supervision.

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Availability of data and materials

The datasets generated and/or analyzed during the current study, including the complete R analysis code, codebook and data dictionary constituting the reproducible analysis pipeline, are available from the corresponding author on reasonable request.

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Figures

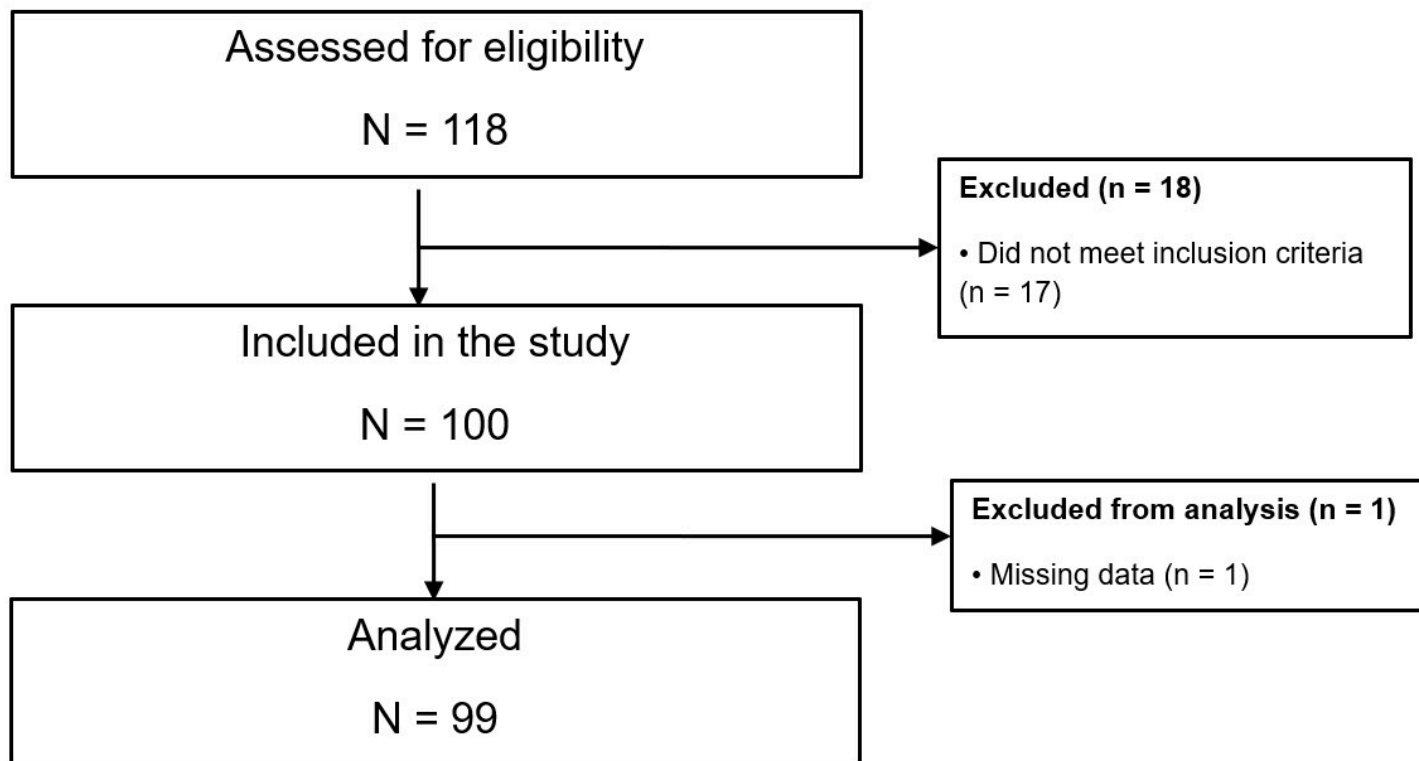


Figure 1

Flow diagram of patient recruitment and study inclusion

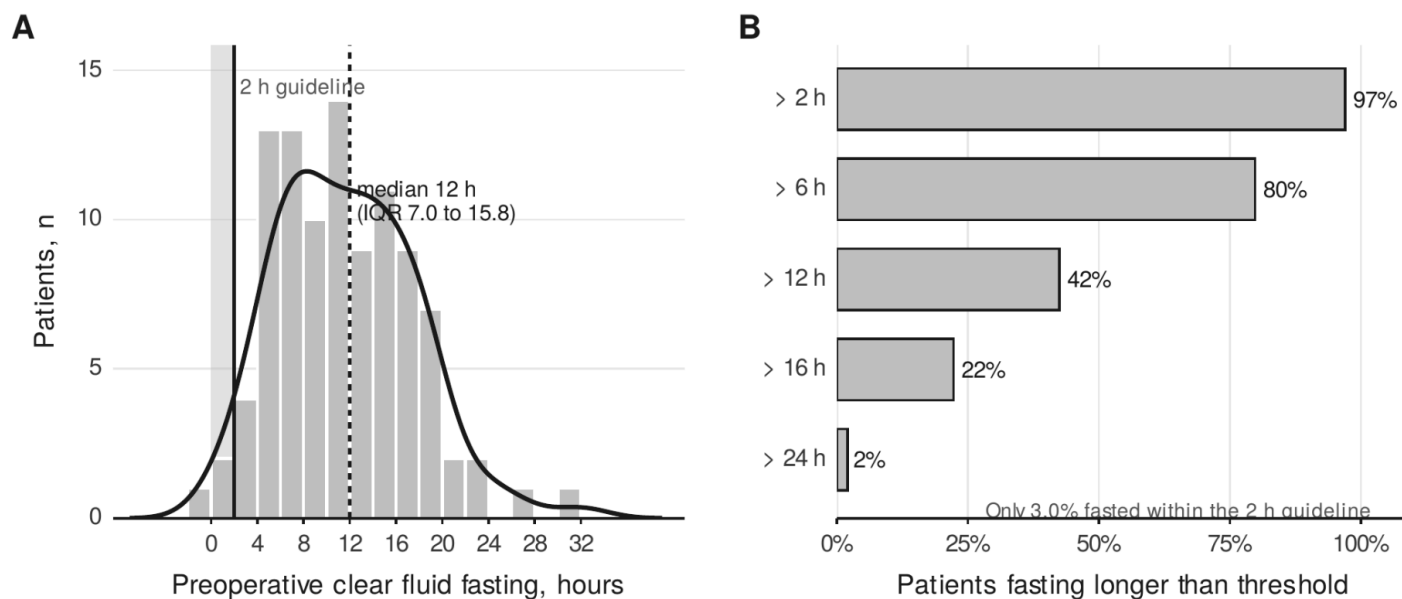


Figure 2

Distribution of preoperative clear fluid fasting duration in 99 liver transplant recipients. (A) Histogram of fasting duration (grey bars) overlaid with a kernel-density curve; the vertical dashed line marks the

median (12.0 h) and the thin vertical line the 2 h guideline limit. **(B)** Share of recipients whose fasting exceeded successive clinical thresholds: 97% fasted longer than 2 hours and 42% longer than 12 hours, whereas only 3.0% (3 of 99) met the recommended 2 h limit.

Abbreviations: CFF, clear fluid fasting.

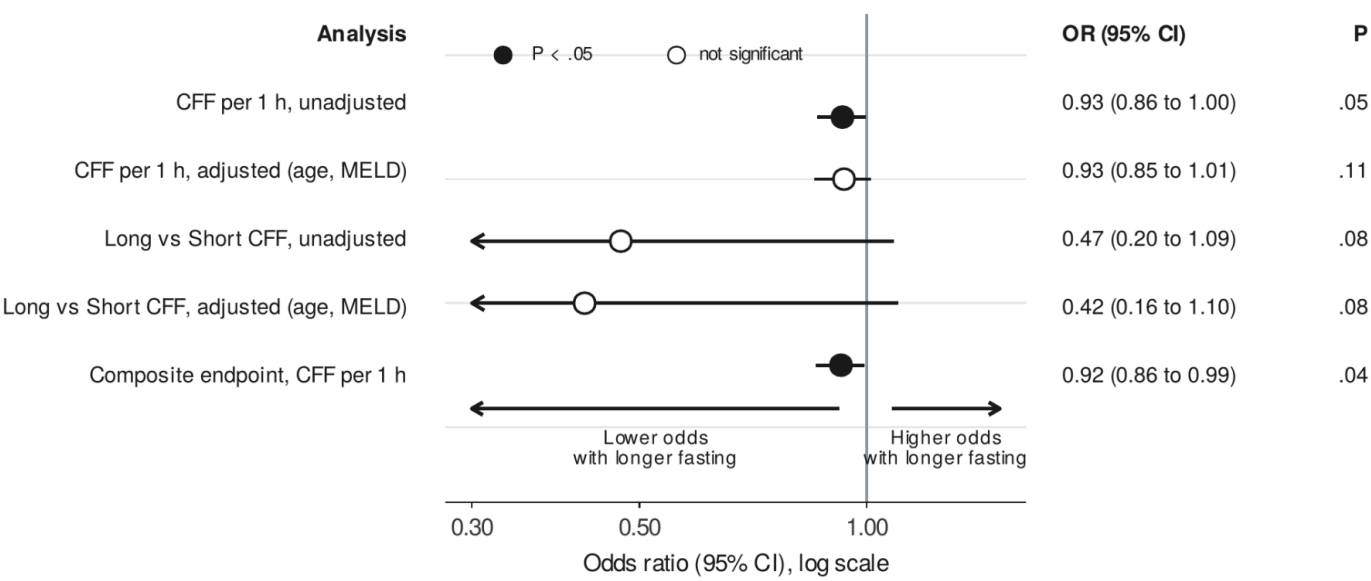


Figure 3

Odds ratios for post-induction hypotension across model specifications. Markers are odds ratios for longer versus shorter fasting on a logarithmic scale, and horizontal whiskers are 95% confidence intervals; a leftward arrowhead indicates a limit extending beyond the plotted range. Filled markers denote a nominally significant estimate ($P < .05$); an odds ratio below the null (1.0) corresponds to lower odds of hypotension with longer fasting. Adjusted models retained age and MELD as a priori covariates (events per variable, 11.7), and the composite endpoint combined hypotension with initiation of ephedrine rescue at induction.

Abbreviations: OR, odds ratio; CI, confidence interval; MELD, Model for End-stage Liver Disease.

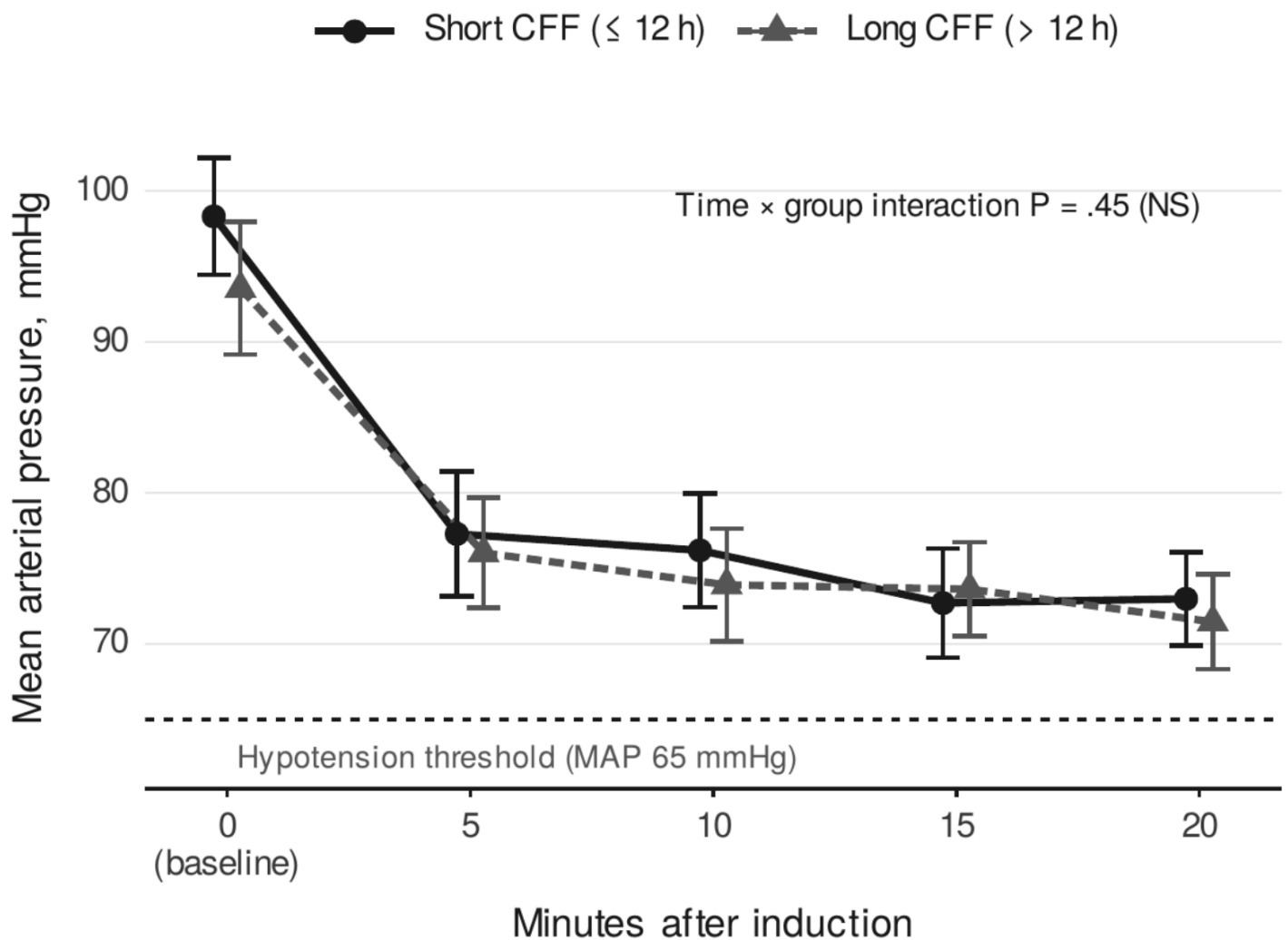


Figure 4

Mean arterial pressure trajectory after induction of anesthesia by clear fluid fasting group. Group mean arterial pressure at baseline and at 5, 10, 15 and 20 minutes after induction (Short CFF, black solid line with circles; Long CFF, grey dashed line with triangles), with 95% confidence intervals shown as error bars laterally offset to prevent overlap; the horizontal dashed line marks the 65 mmHg hypotension threshold. A linear mixed-effects model demonstrated no time-by-group interaction ($P = .45$), indicating parallel trajectories.

Abbreviations: MAP, mean arterial pressure; CFF, clear fluid fasting.

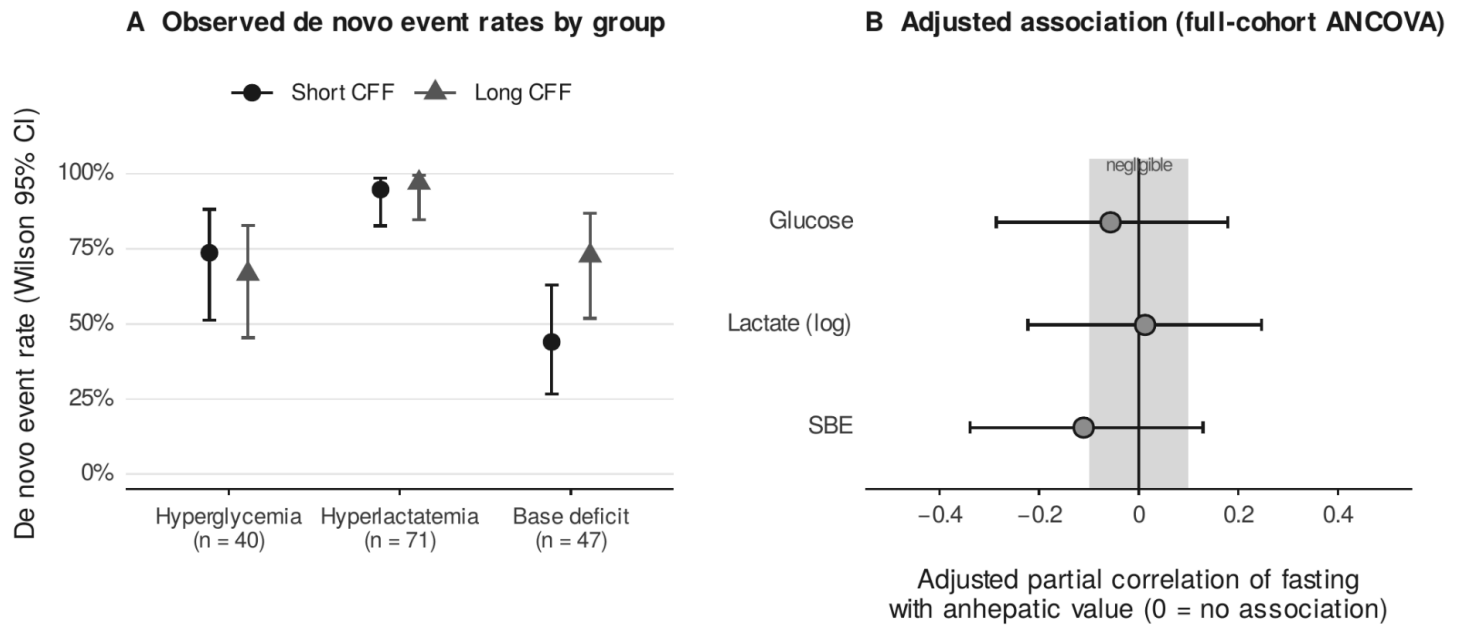


Figure 5

Clear fluid fasting and intraoperative metabolic outcomes. (A) Observed de novo metabolic event rates by fasting group (Short CFF, black circles; Long CFF, grey triangles) with Wilson 95% confidence intervals; the eligible cohort size is given beneath each outcome. A de novo event required a normal baseline value together with an available anhepatic-phase measurement crossing the abnormality threshold. **(B)** Adjusted association from the full-cohort analysis of covariance: each marker is the partial correlation between fasting duration and the labelled anhepatic value, adjusted for the corresponding baseline value, age, MELD and sex, with 95% confidence intervals; the shaded band marks the negligible range (absolute r below 0.1). Every estimate lies within or across this band, and the full-cohort specification avoids the selection and collider bias inherent in conditioning on a normal baseline.

Abbreviations: CFF, clear fluid fasting; MELD, Model for End-stage Liver Disease; SBE, standard base excess.

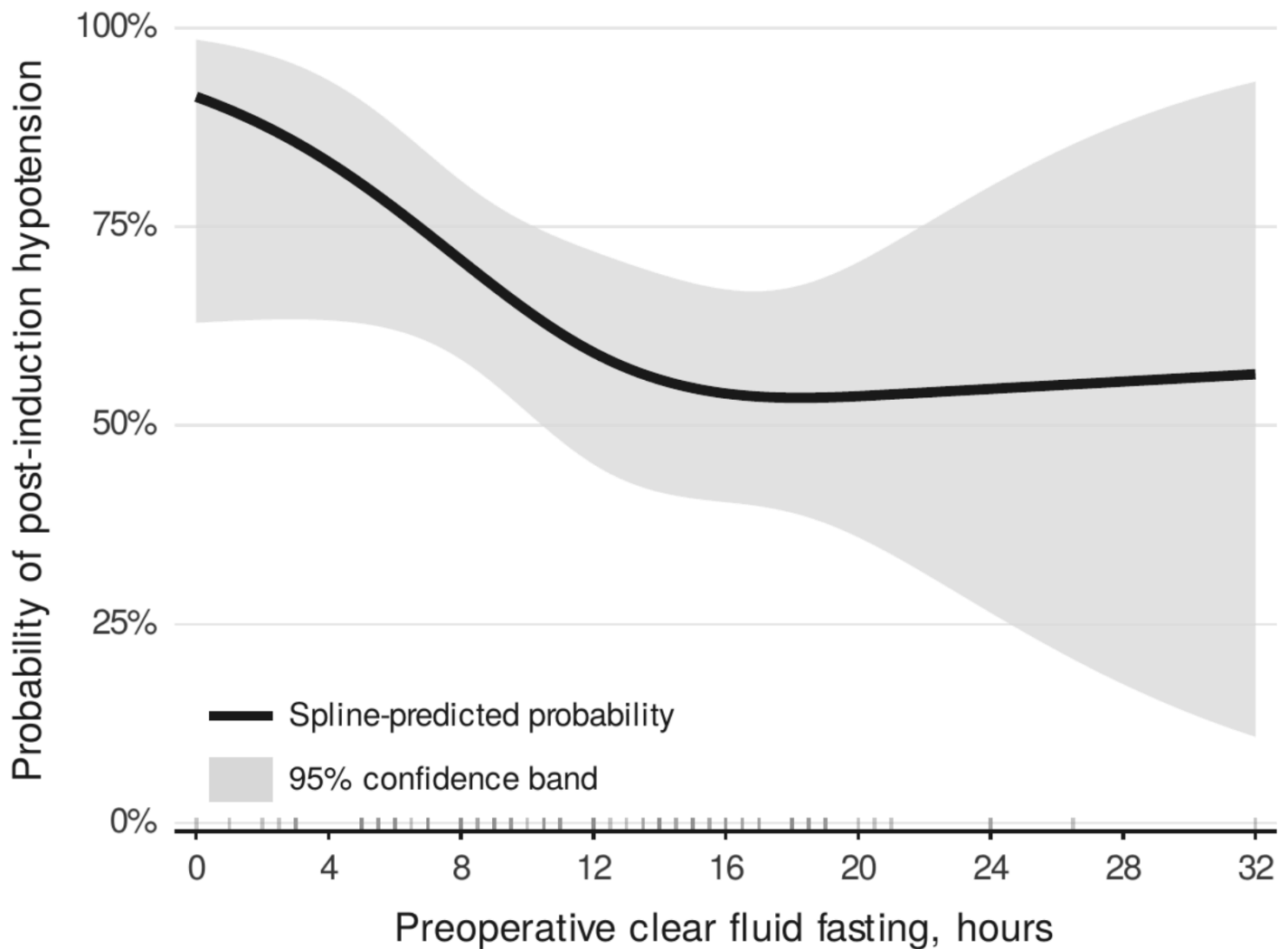


Figure 6

Dose–response relationship between continuous clear fluid fasting duration and post-induction hypotension. The solid curve is the adjusted probability of post-induction hypotension from a logistic model with a restricted cubic spline (3 knots) for fasting duration, and the shaded region is its pointwise 95% confidence band; tick marks along the horizontal axis (rug) denote the fasting duration of each patient. Hypotension was defined as a mean arterial pressure below 65 mmHg or a decrease exceeding 30% from the first post-induction reading, recorded 5 to 20 minutes after induction.

Abbreviations: MAP, mean arterial pressure.

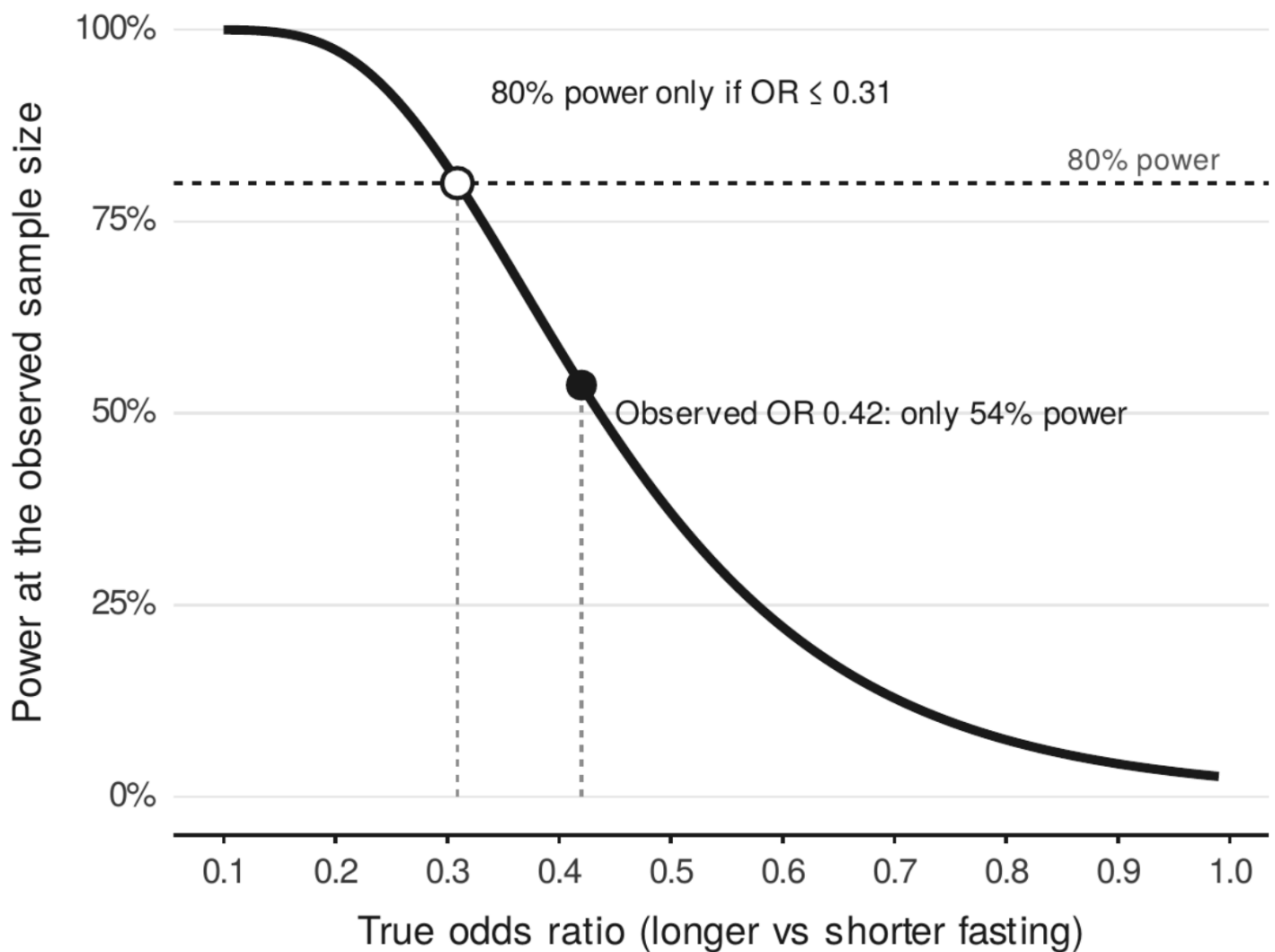


Figure 7

Design sensitivity of the post-induction hypotension analysis. Statistical power attainable at the realized sample size (57 versus 42 patients; reference event rate 71.9%) as a function of the assumed true odds ratio. The study would reach 80% power (horizontal dashed line) only for an odds ratio of 0.31 or smaller (open marker); the observed adjusted odds ratio of 0.42 corresponded to only 54% power (filled marker). Power here is a fixed property of the design and must not be conflated with a post-hoc observed-power calculation.

Abbreviations: OR, odds ratio.

Supplementary Files

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