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Cardiac output-guided vs. mean arterial pressure-guided hemodynamic management in craniotomy patients with cardiovascular disease: a randomized trial

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We tested the primary hypothesis that cardiac output (CO)-guided versus mean arterial pressure (MAP)-guided hemodynamic management reduces the fraction of patients with 90-day Glasgow Outcome scores ≤ 4 (on a 1–5 scale, 5 better) after supratentorial brain tumor resections in adults with cardiovascular disease. 202 adults were randomized to intraoperative hemodynamic management guided by either CO or MAP. In patients assigned to CO guidance, clinicians targeted CO > 4 L/min and > 90% of baseline values using a combination of fluids and vasoactive agents. In patients assigned to MAP guidance, clinicians targeted MAP within ± 20% of baseline and ≥ 65 mmHg. Patients randomized to CO guidance were given more crystalloid and vasoactive support, resulting in significantly higher intraoperative CO and MAP. The proportion of patients with unfavorable 90-day Glasgow Outcome Scores (≤ 4) was non-significantly lower in the CO group (34% vs. 45%, *P* = 0.112). However, CO-guided management significantly reduced the incidence of postoperative cerebral edema (3% vs. 11%), reduced new neurological events (27% vs. 44%), and shortened hospitalization (median 8 vs. 9 days). While encouraging, findings from our small should be considered exploratory and warrant confirmation in adequately powered trials.

Keywords Anaesthesia, Cardiovascular disease, Supratentorial brain tumor resection, Cardiac output, Hemodynamic management, Mean arterial pressure

In patients undergoing brain tumor resection, postoperative complications remain common and clinically significant. Prospective observational studies report that 31% of patients experience at least one postoperative complication within the early postoperative period, with neurological complications accounting for 16% of all cases[1]. Furthermore, large multicenter cohort studies have demonstrated that severe neurological complications alone occur in 11% of patients undergoing brain tumor craniotomy[2]. Complications are associated with prolonged hospitalization, delayed neurological recovery, and healthcare utilization. Among patients with preexisting cardiovascular diseases, hemodynamic fluctuations are pronounced regardless of preoperative control status[3,4]. Vulnerability arises from pathophysiological alterations. Impaired diastolic reserve limits cardiac adaptation to preload changes, increasing sensitivity to fluid shifts and anesthetic vasodilation[5]. Concurrent autonomic dysfunction attenuates baroreflex responses, reducing the capacity to maintain perfusion under surgical stress[6].

Patients with cardiovascular disease having craniotomies represent a physiologically distinct and particularly vulnerable population. Neurosurgery per se frequently compromises perfusion and impairs baroreflex sensitivity

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and cerebral autoregulation[7], and underlying cardiac dysfunction (including reduced systolic or diastolic reserve), which limits the ability to augment cardiac output in response to surgical stress[8]. Chronic cardiovascular conditions such as hypertension further shift and narrow the cerebral autoregulation curve, rendering cerebral blood flow more pressure-passive and increasingly dependent on systemic blood flow rather than arterial pressure alone[9]. Therefore, craniotomy patients often exhibit impaired baroreflex sensitivity and cerebral autoregulation, rendering cerebral perfusion directly dependent on hemodynamic parameter stability[10–14].

The optimal hemodynamic management strategy for preserving cerebral perfusion remains controversial. Mean arterial pressure (MAP) is commonly used as a surrogate for cerebral perfusion, although the relationship is inconsistent[14]. For example, administration of phenylephrine, a selective α-adrenergic agonist, increases MAP primarily through systemic vasoconstriction. However, when cerebral autoregulation is impaired, vasoconstriction-induced increases in MAP do not reliably translate into improved cerebral microcirculatory perfusion and may even reduce cerebral blood flow by decreasing cardiac output (CO) and global blood flow[15]. Moreover, the cerebrovascular effects of phenylephrine are critically modulated by arterial carbon dioxide tension and the integrity of cerebral autoregulation[15]. Accordingly, MAP alone is an imperfect surrogate for cerebral tissue-level perfusion, particularly in the presence of vasoactive agents or in patients with impaired autoregulatory capacity.

In contrast, CO correlates more closely with cerebral perfusion than MAP because increases in CO enhance cerebral blood flow even without changes in MAP[16]. Nonetheless, trials of hemodynamic management guided by CO report both positive[17,18]and neutral[19,20]results. Inconsistent findings likely reflect substantial heterogeneity across reported trials including differences in patient baseline risk, CO optimization thresholds and intervention algorithms, timing and duration of hemodynamic guidance, and outcomes that range from surrogates to clinically meaningful events[21].

We therefore sought to determine whether hemodynamic management guided by CO rather than MAP during supratentorial brain tumor resections improves neurological outcomes in patients with cardiovascular disease. Specifically, We tested the primary hypothesis that CO-guided versus MAP-guided hemodynamic management reduces the fraction of patients with 90-day Glasgow Outcome scores ≤ 4 (on a 0–5 scale, 5 better) after supratentorial brain tumor resections in adults with cardiovascular disease. Secondarily, we tested the hypotheses that CO-guided hemodynamic management reduces the incidence of postoperative cerebral oedema, reduces new neurological events, reduces postoperative cardiovascular events, shortens the duration of hospitalization, and improves Glasgow Coma scores at hospital discharge.

Materials and methods

Study design

Our trial was approved by the Ethics Committee of Xiangya Hospital in May 2019 (Approval No. 201905134). All methods were performed in accordance with the relevant guidelines and regulations, including the Declaration of Helsinki and institutional requirements. Written informed consent was obtained from all patients. This trial was reported in accordance with the CONSORT 2010 guidelines. Patients were recruited from July 29, 2019 to January 13, 2022 at Xiangya Hospital of Central South University, China. During this period, 2,378 patients were screened, and 202 patients meeting the predefined inclusion criteria were enrolled and randomized, as detailed in the CONSORT flow diagram (Fig. 2). The trial was registered with the Chinese Clinical Trials Registry (registration number: ChiCTR1900024660, https://www.chictr.org.cn/) on July 20, 2019, prior to the first patient enrollment (July 29, 2019).

Study participants

Adults ≥ 18 years old scheduled for elective supratentorial brain tumor resections who had coexisting cardiovascular disease were eligible for trial inclusion. We defined cardiovascular disease by previously diagnosed hypertension, coronary artery disease (with or without angina pectoris), ventricle dysfunction (as documented by preoperative transthoracic echocardiography, defined as CO < 4 L/min, or/ and ejection fraction < 50%), cardiomyopathy, congenital heart disease, moderate or severe valvular disease, or symptomatic arrhythmia.

Participants were excluded if they met any of the following conditions: American Society of Anesthesiologists classification status IV or V, severe hepatic or renal dysfunction (serum creatinine concentrations > 300 μmol/L or aspartate aminotransferase or alanine aminotransferase > 1.5 times the upper limit of normal), moderate-to-severe pulmonary function impairment, defined as a preoperative FEV1 < 80% predicted and/or DLCO < 60% predicted on standard pulmonary function testing, or documented pulmonary disease assessed by the treating physician to confer significant perioperative respiratory risk, history of alcohol or substance abuse disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), based on preoperative medical records and clinical assessment, or inability/unwillingness to comply with study protocols.

Intraoperative study protocol and measurement

All patients had routine monitoring and a radial arterial catheter was inserted. Advanced hemodynamic variables were estimated from intra-arterial pressure waveforms by FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA) hemodynamic monitors, and included CO, cardiac index, MAP, stroke volume, stroke volume variation[22–24].

Baseline hemodynamic measurements were obtained before anesthetic induction. Anaesthesia was induced with midazolam, sulfentanil, etomidate, cisatracurium, and propofol. Anaesthesia was maintained with propofol, cisatracurium, remifentanil and sevoflurane. Hypnotic depth was estimated by PSI 25–50 processed electrooculographic monitoring (SedLine, Masimo Inc, Irvine, CA). Tidal volume and respiratory rate were adjusted to maintain $EtCO_2$ 30–35 mmHg. Crystalloid and colloid infusions were used for hemodynamic stability, and blood was transfused when hemoglobin was < 80 g/L.

Mannitol (20%, 1 g/kg) was infused within 15 min after scalp incision. Brain relaxation upon opening of the dura was evaluated by a single experienced neurosurgeon who was blinded to group assignment on a 4-point scale: grade 1, perfectly relaxed; grade 2, satisfactorily relaxed; grade 3, firm brain; grade 4, bulging brain. A second bolus of 0.5 g/kg mannitol was permitted if brain relaxation remained ≥ grade 3 after the initial dose[25].

Randomization and masking

Randomization was computer-generated with permuted block randomization (block size of 4, allocation ratio 1:1). Allocation was concealed in sealed opaque envelopes that were opened shortly before anesthetic induction. Anesthesiologists could not be blinded to treatment, but patients, surgeons, and investigators were blinded to randomization and relevant variables. 90 days neurological outcomes were assessed by trained research staff blinded to group allocation using a standardized telephone-based GOS interview.

In patients randomized to CO guidance, individualized hemodynamic management targeted CO above 90% of baseline and > 4 L/min. This dual-threshold strategy was designed to protect against both absolute and relative hypoperfusion. The absolute threshold (4.0 L/min) reflects a physiologically reasonable lower limit of CO in anesthetized adults[26], whereas the relative threshold (≥ 90% of baseline) was intended to preserve patient-specific perfusion requirements in a heterogeneous population with cardiovascular comorbidities[21]. Cardiovascular agents and fluids were given with the goal of keeping CO within the target range. The guidance strategy focused on dynamic adjustments based on key hemodynamic variables including stroke volume variation and cardiac index. Interventions were tailored to optimize preload, enhance contractility with inotropic drugs, or adjust anaesthesia depth and afterload as necessary to maintain hemodynamic stability (Fig. 1).

In patients randomized to MAP guidance, hemodynamic management targeted MAP within ± 20% of baseline and > 65mmHg. The FloTrac/Vigileo hemodynamic monitor screen was fully obscured throughout the intraoperative period, rendering all CO-derived variables including CO, SV, stroke volume variation (SVV), cardiac index, and systemic vascular resistance. Clinicians thus provided MAP guidance and based intraoperative decisions solely on standard variables including electrocardiography, arterial blood pressure, oxygen saturation, and $EtCO_2$.

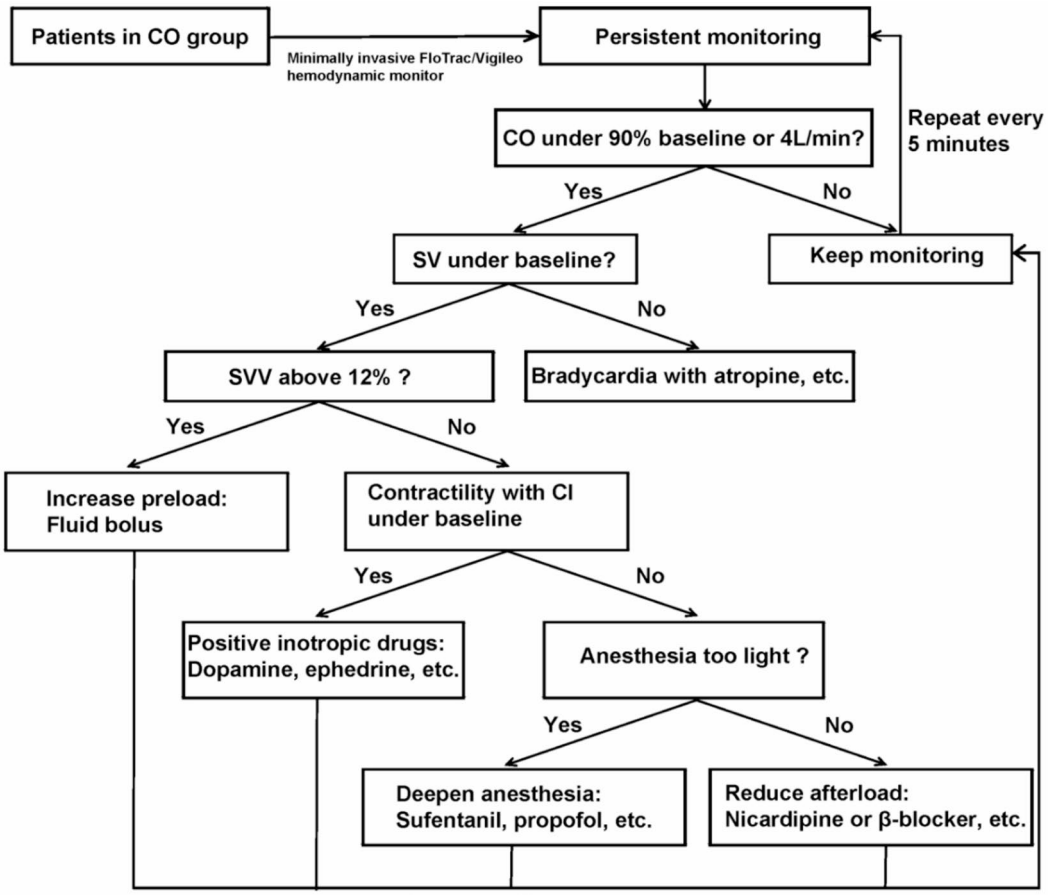

Fig. 1. Protocols of individualized CO-guided care. CO, cardiac output; SV, stroke volume; SVV, stroke volume variation, CI, cardiac index.

Study primary outcome and secondary outcomes

Our primary outcome was the fraction of patients with Glasgow Outcome scores ≤ 4 at 90 days after surgery. The Glasgow Outcome scores was selected because it is a validated patient-centered measure of global functional recovery after brain injury that reflects both disability and social participation[27]. Although 90 days represents a distal outcome influenced by multiple factors beyond the intraoperative period, long-term functional status is the most clinically meaningful endpoint for patients recovering from brain tumor surgery[28]. Furthermore, the use of a 3-month functional outcome is consistent with prior neurosurgical and neurocritical care studies, facilitating comparison across trials and interpretation within the broader literature[29]. The GOS ranges from 1 (death) to 5 (good recovery), where higher scores indicate better outcomes. A change of at least 1 point on the GOS score is generally considered clinically meaningful[27].

Secondary outcomes included postoperative hospital stay, postoperative emerging cerebral oedema, new neurological and cardiovascular events. Emerging cerebral oedema was diagnosed radiologically using a standardized postoperative non-contrast head CT scan performed approximately 2 h after surgery. Edema was defined as a newly developed hypodense area adjacent to the surgical site compared with preoperative imaging, accompanied by radiological signs of mass effect (e.g., sulcal effacement or midline shift)[30,31], as assessed by a neurosurgeon and/or neuroradiologist blinded to group allocation.

Neurological events were defined as any new deficit and were analyzed as a collapsed composite secondary outcome. Eligible events included focal seizure, new muscle weakness, disorientation, aphasia, and visual disturbance (Supplementary File 1). Neurological events were further subclassified as total events and those that remained symptomatic at discharge. "Remained symptomatic" was defined as persistence of the associated neurological deficit or symptom at the time of hospital discharge, without recovery to the patient's preoperative baseline. Additionally, the Glasgow Coma Scale score[32]at discharge, ranging from 3 (deep coma) to 15 (fully alert), was used for bedside assessment of the conscious level, a key clinical feature of acute brain injury.

Postoperative patients were assessed daily. Active postoperative monitoring was performed from postoperative day 1 until hospital discharge, including structured bedside neurological examinations conducted by neurosurgeons or trained study personnel. Consciousness and orientation were evaluated using the Glasgow Coma Scale, while motor deficits were assessed using the Medical Research Council muscle strength scale. Electroencephalography was used as an adjunctive test to confirm suspected focal seizures. Additional adverse outcome data were collected from the medical records, imaging examination, laboratory tests, etc. Diagnosis of postoperative complications was based on the criteria of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision and listed in Supplementary file 1. Adverse event monitoring was performed by members of the study team and reviewed by the principal investigator at regular intervals.

Hospital discharge criteria included stable cardiac rhythmic, ability to tolerate oral fluid and solid food, adequate pain control without the need for intravenous analgesia, independent mobilization, temperature within a normal range, established urination and defecation, no drainage tubes, normal wound healing, no major complications, and laboratory tests within normal limits.

Statistical analysis

Our previous study involving 126 patients with cardiovascular disease demonstrated that 62% achieved a favorable outcome (GOS score of 5) at 3 months post-craniotomy[33]. Our hypothesis was that CO-guided hemodynamic management improves the proportion of patients achieving a favorable outcome (GOS score = 5) by a relative 30% from an anticipated baseline of 62% as observed previously, corresponding to an expected increase from 62% to 81%, representing an absolute difference of 19%. Based on a two-sided alpha of 0.05, 80% power, and 10% anticipated dropouts, 101 patients per group were required.

Descriptive statistics were calculated for baseline and perioperative characteristics and outcomes. The Kolmogorov-Smirnov and Shapiro-Wilk test was used to assess the normality of the measurement data. Data with skewed distributions were reported as medians (P25, P75), including age, CO, MAP, surgical duration, postoperative hospital stay, Glasgow Coma score, etc. Categorical variables were presented as frequencies (percentage) including preoperative cardiovascular complications, intraoperative use of vasoactive drugs, postoperative adverse events, etc.

Baseline characteristics were compared using absolute standardized differences (ASDs), defined as the absolute difference in means, medians, or proportions divided by the pooled standard deviation. Baseline variables were considered imbalanced when the ASD exceeded $1.96 \times \sqrt{\frac{1}{\mathbf{n_1}} + \frac{1}{\mathbf{n_2}}} \geq 0.4$ and would be adjusted for in all analyses.

For the primary outcome, GOS ≤ 4 was expressed as n (%), and differences between the groups compared using chi-square tests and effect sizes reported as risk ratios with 95% confidence intervals. In addition, GOS was analyzed as an ordinal variable: median scores were compared using the Wilcoxon rank-sum test with Hodges–Lehmann estimates for median differences, and the full distribution of GOS categories was compared using chi-square tests. To fully account for the ordinal nature of GOS, a proportional odds logistic regression model was further applied, with results expressed as adjusted common odds ratios and 95% confidence intervals.

Secondary continuous variables including Glasgow Outcome scores were compared using the Wilcoxon rank-sum test. Hodges-Lehmann estimation was used to calculate the confidence interval for the median difference. Binary variables were evaluated using chi-square or Fisher exact tests with effect quantified as risk ratios and 95% confidence interval. The confidence interval for difference in proportions were estimated using Newcombe's method with continuity correction. No formal adjustment for multiple comparisons was applied to secondary outcomes, which were prespecified and analyzed in an exploratory manner using nominal two-sided P values.

Most pre-specified subgroup interaction analyses for the primary outcome were conducted using clinically meaningful cutoffs. Specifically, age was categorized as ≥ 65 years; body mass index as ≥ 25 kg/m^2; blood urea

nitrogen as >7.1 mmol/L; baseline CO as <4.0 L/min; and serum albumin as <40 g/L. For variables lacking established clinical dichotomization thresholds or where diagnostic cutoffs yielded insufficient subgroup sizes, median-based categorization was retained for exploratory analyses. Additional criteria included American Society of Anesthesiologists classification (II vs. III), New York Heart Association classification (I vs. II/III), and baseline Barthel's score (100 vs. <100).

Analyses used SPSS 22.0 statistical software and R (version 4.0.1) packages, including tableone, forestplot, and readxl. P-values less than 0.050 was considered statistically significant.

Results

Baseline data

After screening and assessment, 202 participants were randomized. Participants demonstrated good adherence to the assigned management strategies without protocol deviations. However, one patient in the MAP-guided group was excluded after randomization because surgery was cancelled, and one patient in the CO-guided group was lost to follow-up during the 90-day period, leading to a final analysis population of 200 patients (Fig. 2). Baseline characteristics were generally well balanced between the two groups, and none exceeded the pre-specified imbalance threshold of 0.4 (Table 1). Additionally, baseline hemodynamic values were similar in each group (Table 2).

Intraoperative MAP distributions were similar in each treatment group, with values concentrated between 80 and 95 mmHg (Fig. 3). However, CO distributions clearly differed, generally being >4 L/min in patients randomized to CO guidance whereas the range was broader in patients randomized to MAP guidance, with many values <4 L/min (Fig. 4). Hemodynamic management guided to CO was thus effective and resulted in groups that distinctly differed.

Perioperative data

Patients randomized to CO guidance demonstrated more stable intraoperative hemodynamic profiles, characterized by higher average intraoperative MAP [90 (83, 98) vs. 84 (79, 90) mmHg, $p < 0.001$], higher CO

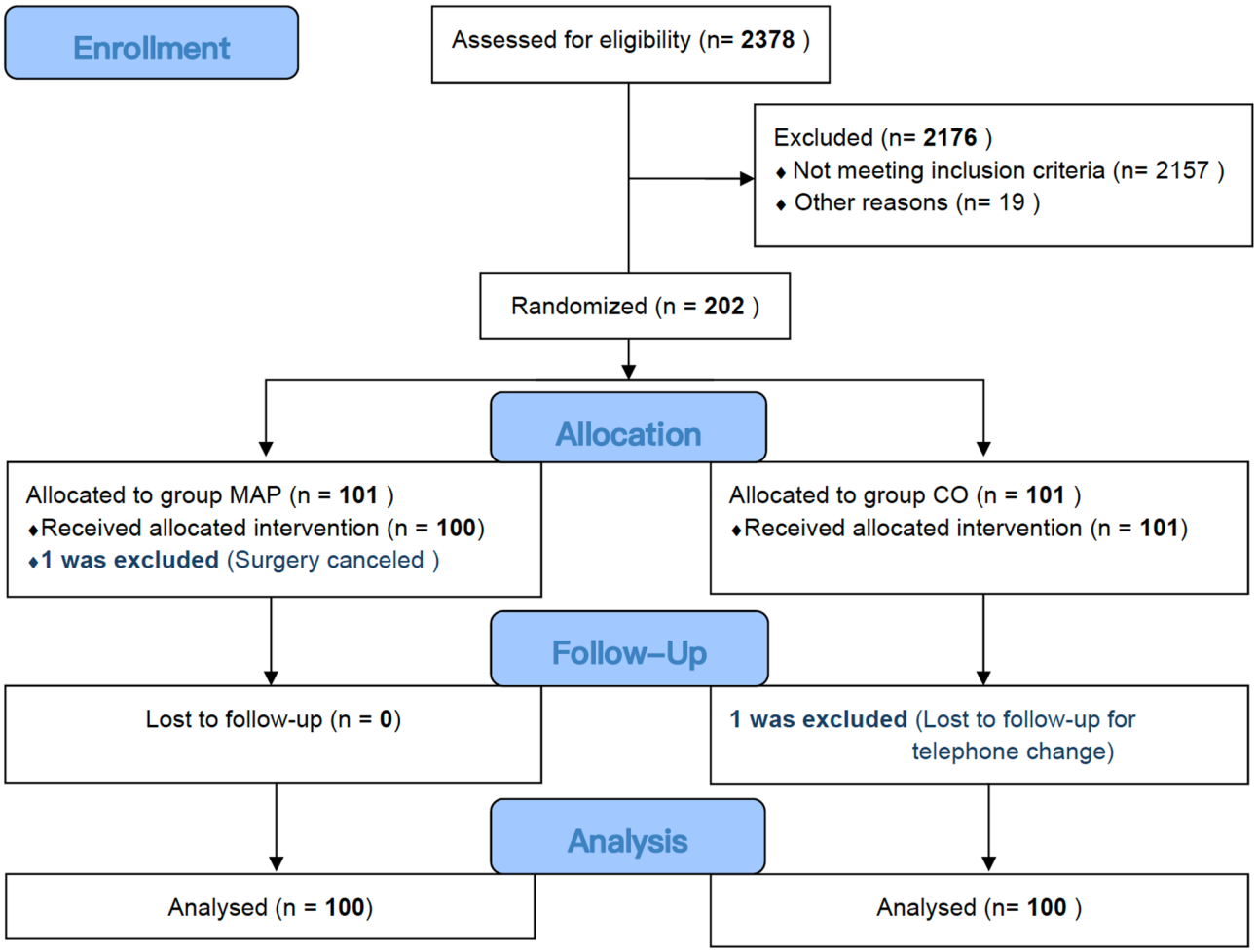

Fig. 2. Flow diagram according to consolidated standards of reporting trials. CO, cardiac output, MAP: mean arterial pressure.

	MAP group ($n=100$)	CO group ($n=100$)	Absolute standardized difference
Age, median (IQR), year	56 (51, 64)	55 (50, 63)	0.087
Female, n (%)	65 (65)	61 (61)	0.083
BMI, median (IQR), kg/m^2	24 (22, 26)	24 (22, 26)	0.025
ASA classification II/III, n	63 / 37	67 / 33	0.084
NYHA classification I/II/III, n	78 / 20 / 2	73/ 25 /2	0.12
Preoperative GCS < 15, n (%)	2 (2)	1 (1)	0.082
Preoperative Barthel's index score, median (IQR)	100 (100, 100)	100 (95, 100)	0.17
Preoperative KPS score, median (IQR)	90 (90, 90)	90 (90, 90)	0.063
Coexisting disease, n (%)			
Hypertension	58 (58)	55 (55)	0.152
Coronary artery disease	28 (28)	30 (30)	
Cardiomyopathy	14 (14)	14 (14)	
Valvular heart disease	0 (0)	1 (1)	
Intracranial tumors			
Glioma/meningioma/others, n	27 / 58 / 15	26 / 61 / 13	0.069
Longest diameter, median (IQR), mm	30 (20, 39)	28 (20, 36)	0.101

Table 1. Demographics and baseline characteristics. The values are presented as median (interquartile range) or n (percentage) depending on the data type. IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; NYHA, New York heart association; GCS, Glasgow coma scale; KPS, Karnofsky Performance Status.

[4.7 (4.3, 5.7) vs. 3.9 (3.1, 4.5) L/min, $p<0.001$], lower stroke volume variation [10 (8, 12) vs. 13 (11, 15)%, $p<0.001$], fewer number of hypotension events [18 vs. 32, $p=0.022$], and fewer patients with CO < **4** L/min [0% vs. 48%, $p<0.001$]. To achieve these targets, the CO-guided group were given more crystalloid input [1.8 (1.4, 2.5) vs. 1.6 (1.2, 2.0) l, $p=0.008$], more required ephedrine (63% vs. 41%, $p=0.002$) and dopamine (21% vs. 3%, $p<0.001$). Other variables were similar in each group including surgery duration, blood loss, and laboratory tests (Table 2).

Trial outcomes

There were fewer patients with Glasgow Outcomes scores ≤ 4 at 90 days after surgery among those assigned to CO-guided than those assigned to MAP-guided hemodynamic management, although not significantly so: 34 (34%) vs. 45 (45%), relative risk 0.76, 95% CI (0.53, 1.07), $P=0.112$. The median GOS score did not differ between groups ($P=0.086$). When GOS was analyzed as an ordinal outcome using a proportional odds model, CO-guided management was not associated with a statistically significant shift toward better functional outcomes (adjusted common odds ratio, 0.61; 95% CI, 0.36–1.07; $P=0.086$). The overall distribution of GOS scores across categories did not differ significantly between groups ($P=0.380$).

Patients randomized to CO guidance were discharged earlier from the hospital [8 (7, 10) vs. 9 (7, 11) days, $p=0.036$], and had fewer cerebral oedema [3% vs. 11%, $p=0.027$] or new-onset neurological events [27% vs. 44%, $p=0.012$]. Other secondary outcomes did not differ significantly between the groups including Glasgow Coma scores at discharge, and postoperative cardiovascular adverse events (Table 3).

The effect of treatment on the number of patients with GOS scores ≤ 4 at 90 days post-surgery was consistent across subgroups including age, body mass index, American Society of Anesthesiologists classification, New York Heart Association classification, tumor characteristics, duration of surgery, baseline CO and MAP, baseline albumin, and baseline creatinine, except for possibly spurious interactions on baseline hemoglobin (P for quantitative interaction = 0.037). Subgroup analysis results are shown in Fig. 5.

Discussion

CO-guided hemodynamic management non-significantly reduced the fraction of patients with Glasgow Outcome scores ≤ 4 at 90 days, from 45% to 34%, corresponding to a relative risk of 0.76 (95% CI, 0.53 to 1.07). Glasgow Outcomes scores, treated ordinally, also did not differ significantly (common odds ratio 0.61, 95% CI 0.36 to 1.07; $P=0.086$). Although both point estimates favored CO-guided management, the confidence intervals were wide, indicating substantial uncertainty regarding the true magnitude of effect. Taken together, our estimates suggest that the true effect could plausibly range from a clinically meaningful benefit to little or no effect. Given the lack of statistical significance for the primary outcome and the imprecision reflected by the confidence intervals, these findings should be interpreted as exploratory signals from an underpowered trial rather than evidence of a definitive clinical effect.

Hemodynamic management guided by CO rather than MAP improved many secondary outcomes. For example, fewer CO-guided patients who had cerebral oedema, fewer had new neurological deficits, and the duration of hospitalization was shorted in CO-guided patients. Shorter hospitalizations in CO-guided patients appears to have been driven by less postoperative cerebral oedema and fewer new-onset neurological deficits — both of which are well-established causes of delayed post-craniotomy discharge. This parallel improvement

	MAP Group ($n=100$)	CO Group ($n=100$)	Median or Proportion Difference (95% CI)*	*P* Value
Surgical profiles				
Surgery time, median (IQR), hour	4.2 (3.2, 5.5)	4.0 (3.2, 5.3)	-0.2 (-0.7 to 0.2)	0.310
Grades of brain relaxation scale, n	2 (1,2)	2 (1,2)	0 (0,0)	0.368
Intraoperative input and output, median (IQR)				
Crystalloid infusion, ml	1600 (1200, 2000)	1800 (1400, 2500)	300 (50 to 500)	**0.008**
Colloid infusion, ml	500 (0, 500)	500 (0, 500)	0 (0 to 0)	0.718
Autologous red blood cells, ml	0 (0, 0)	0 (0, 100)	0 (0 to 0)	0.400
Urine output, ml	700 (500, 1000)	800 (575, 1250)	150 (0 to 300)	**0.008**
Estimated blood loss, ml	200 (175, 400)	200 (125, 400)	0 (-50 to 50)	0.913
Patients needing a transfusion, n (%)	13 (13)	7 (7)	-0.06 (-0.14 to 0.02)	0.157
Cardiovascular agents administered, n (%)				
Ephedrine	41 (41)	63 (63)	0.22 (0.08 to 0.36)	**0.002**
Dopamine	3 (3)	21 (21)	0.18 (0.09 to 0.27)	**<0.001**
Phenylephrine	14 (14)	11 (11)	-0.03 (-0.12 to 0.06)	0.521
Atropine	12 (12)	12 (12)	0.00 (-0.09 to 0.09)	>0.999
Antihypertensive	7 (7)	12 (12)	0.05 (-0.03 to 0.13)	0.228
Hemodynamic data, median (IQR)				
MAP, mmHg				
Baseline	100 (91, 104)	100 (94, 106)	2 (-1 to 5)	0.197
Intraoperative average	84 (79, 90)	90 (83, 98)	5 (3 to 8)	**<0.001**
CO, L/min				
Baseline	4.9 (3.9, 6.0)	4.8 (3.9, 5.6)	-0.1 (-0.5 to 0.2)	0.573
Intraoperative average	3.9 (3.1, 4.5)	4.7 (4.3, 5.7)	0.8 (0.8 to 1.4)	**<0.001**
SVV, %				
Baseline	14 (11, 18)	14 (11, 17)	0 (-1 to 1)	0.551
Intraoperative average	13 (11, 15)	10 (8, 12)	-3 (-4 to -2)	**<0.001**
Heart rate, beats / min				
Baseline	66 (57, 77)	65(57, 75)	-1 (-4 to 2)	0.557
Intraoperative average	61 (56, 68)	60 (56, 64)	-1 (-3 to 1)	0.276
Intraoperative adverse events, n (%)				
Hypotension †	32 (32)	18 (18)	-0.1 (-0.3 to -0.0)	**0.022**
Low CO	48 (48)	0 (0)	-0.48 (-0.58 to -0.38)	<0.001
Arrhythmia *	5 (5)	5 (5)	-0.00 (-0.06 to 0.06)	>0.999
Laboratory test data, median (IQR)				
Hemoglobin, g/L				
Baseline	132 (122, 142)	132 (125, 139)	0 (-4 to 3)	0.833
End of the operation	120 (108, 132)	119 (110, 129)	0 (-5 to 4)	0.919
Lactate, mmol/L				
Baseline	1.2 (1.0, 1.9)	1.4 (1.0, 1.9)	0.1 (-0.1 to 0.2)	0.428
End of the operation	1.3 (0.9, 1.8)	1.1 (0.9, 1.2)	-0.2 (-0.4 to -0.1)	**0.001**
Albumin, g/L				
Baseline	42 (40, 43)	42 (40, 44)	0 (-1 to 1)	0.499
End of the operation	36 (33, 38)	37 (34, 40)	1 (-1 to 2)	0.289
Alanine aminotransferase, U/L				
Baseline	19 (14,28)	20 (14, 27)	0 (-3 to 3)	0.947
End of the operation	16 (12, 22)	19 (12, 28)	2 (-1 to 4)	0.207
Aspartate Aminotransferase, U/L				
Baseline	20 (17, 26)	20 (17, 24)	-1 (-2 to 1)	0.601
End of the operation	20 (15, 25)	20 (15, 29)	1 (-2 to 3)	0.503
Creatinine, preoperative, μmol/L				
Continued				

	MAP Group ($n=100$)	CO Group ($n=100$)	Median or Proportion Difference (95% CI)*	*P* Value
Surgical profiles				
Baseline	72 (63, 82)	76 (61, 86)	2 (-3 to 6)	0.431
End of the operation	72 (61, 79)	70 (60, 88)	1 (-5 to 6)	0.758
Urea nitrogen, mmol/L				
Baseline	5.4 (4.3, 6.8)	5.1 (4.1, 6.1)	-0.2 (-0.7 to 0.2)	0.302
End of the operation	4.6 (3.7, 5.6)	4.4 (3.4, 5.8)	-0.1 (-0.5 to 0.4)	0.699

Table 2. Perioperative data. The values are presented as median (interquartile range) or n (percentage) depending on the data type. CI, confidence interval; IQR, interquartile range; CO, cardiac output; SVV, stroke volume variation; MAP, mean arterial pressure. † Hypotension was defined as mean arterial pressure lower than 65 mmHg for at least 5 min, requiring vasoactive agents support, with each episode counted separately, even within the same patient. †† Low CO was defined as an intraoperative average CO that is less than 90% of the baseline and lower than 4 L/min. * Arrhythmia was defined as persistent atrial fibrillation and frequent ventricular premature beat.

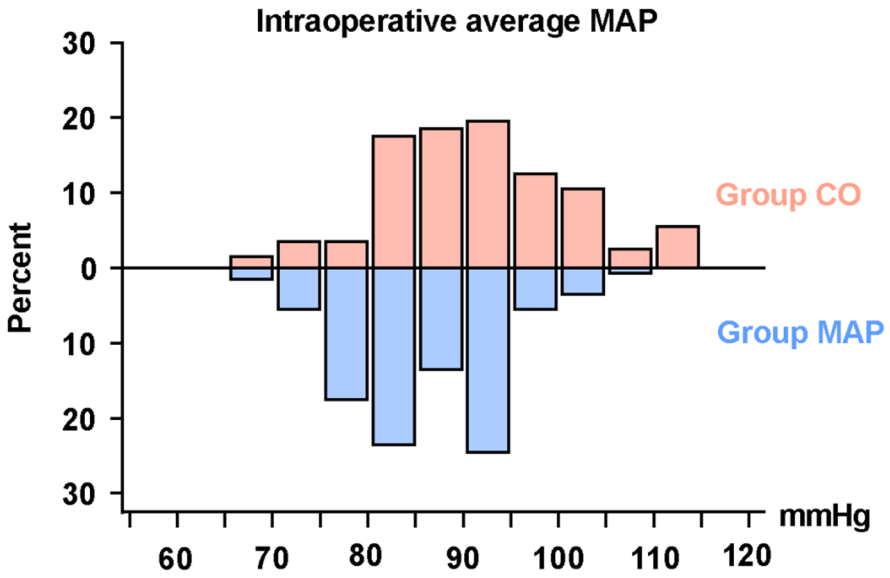

Fig. 3. Intraoperative average mean arterial pressure distribution. The histogram shows the distribution of intraoperative average mean arterial pressure in the patients allocated to cardiac output (pink) and mean arterial pressure (blue) guidance. CO, cardiac output, MAP, mean arterial pressure.

across clinically linked endpoints indicates that the reduced length of stay reflects a smoother neurological recovery trajectory, a point of clear clinical and healthcare resource importance. Together, these findings suggest that CO-guided management may well be helpful in patients at cardiovascular who have intracranial tumor resections. But that said, small trials tend to over-estimate treatment effect[34,35]. Robust trials are needed to confirm benefit and accurately quantify its magnitude.

Most goal-directed fluid management trials in neurosurgical patients were based on stroke volume variation[36,37], end-diastolic volume[38], and MAP[10]. These approaches were largely developed and validated in general neurosurgical populations without systematic consideration of underlying cardiac reserve. For these patients, MAP-guided strategies—particularly those incorporating individualized targets—represent an important advance over fixed pressure thresholds. But they nonetheless remain inherently pressure-oriented and rely on the assumption that the relationship between arterial pressure and cerebral blood flow is preserved. The challenge is that even individualized MAP targets can fully substitute for flow-based hemodynamic optimization in patients with impaired cardiac reserve or altered ventriculo–arterial coupling. For example, in patients with chronic hypertension, or impaired ventricular function, adequate MAP can be maintained through increased systemic vascular resistance despite insufficient forward flow and oxygen delivery[1321]— potentially masking flow-limited cerebral hypoperfusion[14]. Furthermore, titrating to stroke volume variation and high MAP can lead to volume load and can reduce cerebral perfusion[15,39–41].

Our trial extends previous work by guiding hemodynamic management to CO, which is more closely related to cerebral perfusion than other measures[14,15,42]. The distinction may be especially important in patients with pre-existing cardiovascular disease who often exhibit impaired myocardial reserve, altered ventriculo–arterial

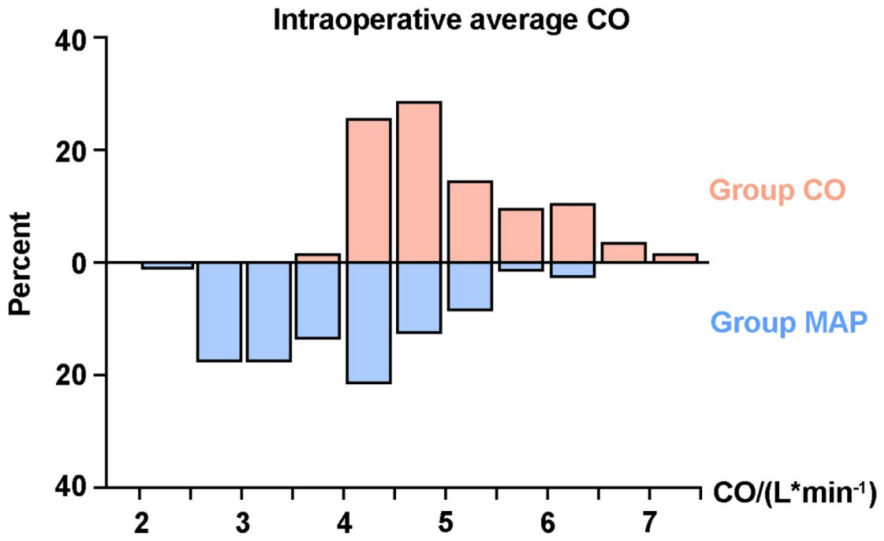

Fig. 4. Intraoperative average cardiac output distribution. The histogram shows the distribution of intraoperative average cardiac output in the patients allocated to cardiac output (pink) and mean arterial pressure (blue) guidance. CO, cardiac output, MAP, mean arterial pressure.

Parameters	MAP Group ($n = 100$)	CO Group ($n = 100$)	Risk Ratio, OR or Median Difference (95% CI)*	*P* Value
Primary outcome				
GOS score 90 days after surgery, median (IQR)	5 (4, 5)	5 (4, 5)	0 (0, 0)	0.086
GOS score: ordinal regression	-	-	OR 0.61 (0.36 to 1.07)	0.086
GOS score 90 days after surgery, n (%)				
5	55 (55)	66 (66)	-	0.380
4	27 (27)	23 (23)		
3	14 (14)	9 (9)		
1–2	4 (4)	2 (2)		
GOS ≤ 4 90 days after surgery, n(%)	45 (45)	34 (34)	0.76 (0.53, 1.07)	0.112
Secondary outcomes				
Postoperative hospitalizaation, median (IQR), days	9 (7, 11)	8 (7, 10)	-1 (-1, 0)	**0.036**
GCS < 15 at discharge, n (%)	10 (10)	4 (4)	0.40 (0.13, 1.23)	0.096
Emerging cerebral oedema, n (%)	11 (11)	3 (3)	0.27 (0.08, 0.95)	**0.027**
New neurological events, n (%)				
Total number	44 (44)	27 (27)	0.61 (0.42, 0.91)	**0.012**
Remained symptomatic before discharge	19 (19)	12 (12)	0.63 (0.32, 1.23)	0.171
Cardiovascular events, n (%)	8 (8)	5 (5)	0.63 (0.21, 1.90)	0.565

Table 3. Primary and secondary outcomes. The values are presented as median (interquartile range) or n (percentage) depending on the data type. CI, confidence interval; IQR, interquartile range; GOS, Glasgow outcome scale; KPS, Karnofsky Performance Status; GCS, Glasgow coma scale; ICU, intensive care unit. * The risk ratio and 95% CI were used to characterize the effectiveness of CO guided hemodynamic treatment for categorical variables.

coupling, and limited ability to augment CO in response to fluid loading or vasopressor therapy[13]. Rather than relying on a single hemodynamic target, we integrated stroke volume, stroke volume variation, cardiac index, and HR to distinguish preload, vasoplegia, and myocardial dysfunction — thus guiding interventions to the dominant physiological derangement. Our multimodal CO-centered strategy may be especially helpful for high-risk neurosurgical patients with cardiovascular comorbidity.

A critical aspect of any trial is control of the exposure because an outcome difference is unlikely without substantive exposure differences. (Trials without meaningful exposure differences represent failed efforts, rather than truly neutral outcomes.) Fortunately, our protocol resulting in two clear groups with substantially higher CO in patients in patients assigned to CO than MAP hemodynamic guidance. In contrast, MAPs were similar

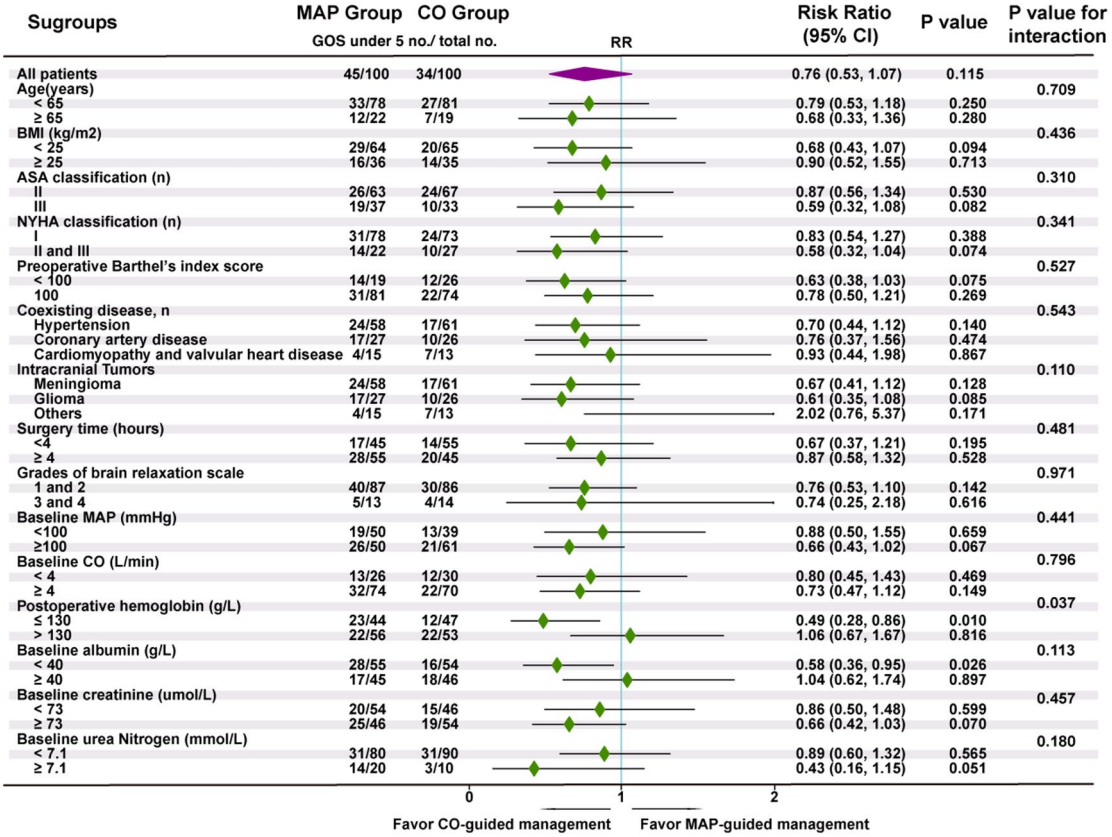

Fig. 5. Risk ratios for Glasgow Outcome Scale scores ≤ 4 in prespecified subgroups. CO, cardiac output, MAP: Mean arterial pressure, BMI, body mass index, ASA, American Society of Anesthesiologists, NYHA, New York heart association.

in each group which is consistent with previous work showing that intraoperative cardiac index and MAP are almost unrelated[43].

In retrospect, GOS scores at 90 days after surgery was an ambitious primary outcome. The GOS score, a comprehensive indicator of neurological recovery, is influenced by multiple factors including tumor characteristics, surgical procedures, postoperative care, and post-discharge rehabilitation[44]. Intraoperative management alone would therefore not be expected to have much influence on such a distal, multi-factorial outcome. In contrast, the effects of beneficial treatment should be apparent in proximal outcomes. Consistent with this theory, individualized CO-guided intervention significantly reduced the incidence of postoperative cerebral oedema, new-onset neurological deficits, and postoperative hospital stay.

Our results and others[45,46]are consistent with the hypothesis that maintaining stable systemic hemodynamics may be associated with neuroprotective effects. For example, improved CO potentially stabilizes intraoperative brain tissue perfusion, particularly in the non-lesioned areas near the surgical site which are at high risk of ischemia-reperfusion injury[47]which can lead to cerebral oedema and secondary brain damage[48,49]. But because cerebral perfusion and blood–brain barrier integrity were not directly measured in this study, these mechanistic interpretations should be considered speculative.

Subgroup analysis suggests that CO-guided individualized hemodynamic management was especially pronounced in patients who had baseline hemoglobin < 130 g/L who presumably have less reserve than those whose blood carries more oxygen[13,50]. These findings are physiologically plausible, as patients with anemia are more likely to experience compromised oxygen delivery or cerebral perfusion, conditions that CO-guided management may help mitigate. Nonetheless, most interactions observed in trials turn out to be spurious and these may be as well.

Our study has several limitations. First, this was a small-scale trial, and future studies with larger sample sizes are needed to validate these findings. Second, due to the nature of the intervention, the attending anesthesiologists could not be blinded to the treatment allocation, potentially introducing performance bias. also, although the study was prospectively registered, the full protocol was not published as a standalone article. This risk was mitigated by strict standardization of perioperative care, protocolized hemodynamic algorithms with explicit physiological targets, and blinding of patients, surgeons, and outcome assessors, with primary and key secondary outcomes being objective or assessed by blinded personnel. Third, various secondary outcomes were analyzed without adjustment for multiplicity, increasing the risk of type I error; our secondary findings should therefore be considered exploratory. Fourth, CO was estimated with the FloTrac/Vigileo system; while widely used, its accuracy may be reduced under conditions of marked vasoplegia or extreme vascular tone,

and results should be interpreted in light of ongoing technological refinement and contemporary validation. Fifty, the selected CO targets (> 4.0 L/min and ≥ 90% of baseline) were physiologically reasonable but were not directly titrated to cerebral perfusion or oxygenation and may not be optimal. Sixth, external validity is limited because different neurosurgical procedures impose distinct pathophysiological and hemodynamic constraints—including brainstem perfusion vulnerability in posterior fossa surgery, rupture–ischemia trade-offs in aneurysm clipping[51], and CPP-driven management in traumatic brain injury[52]—and the incremental benefit of CO-guided management may be attenuated in patients with preserved cardiac function. And lastly, we did not estimate cerebral tissue oxygenation, say with near-infrared spectroscopy. It thus remains uncertain whether optimizing CO actually improved cerebral oxygenation.

Future research should further test the mechanistic and translational implications of our findings. Prior work has linked CO to cerebral oxygenation during neurosurgery[42], and optimized intraoperative fluid management to reduced postoperative cerebral oedema and neurological complications[30,36]. Building on these observations, trials incorporating multimodal cerebral monitoring—such as near-infrared spectroscopy and perfusion imaging—are needed to determine whether CO-guided management causally improves cerebral perfusion, preserves blood–brain barrier integrity, and mitigates ischemia–reperfusion–related injury[53]. From a translational perspective, CO-guided hemodynamic management is feasible using minimally invasive arterial waveform analysis, but widespread adoption will require clinician training, protocolized algorithms, and integration with clinical decision-support systems. Although additional monitoring costs are incurred, these may be offset by reductions in postoperative complications and hospital length of stay in high-risk patients. Future research should therefore evaluate both mechanistic outcomes and cost-effectiveness to define the clinical value of CO-guided strategies.

In conclusion, intraoperative hemodynamic management guided by CO non-significantly improved GOS score at 90 days. CO-guided hemodynamic management was associated with fewer postoperative neurological complications and a shorter hospital stay. However, our single-center trial was small and the results we present should be considered exploratory.

Data availability

Trial data are available collaboratively from the corresponding author upon reasonable request.

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Author contributions

EW: Study design, quality control, and final manuscript approval; NC and MJY: Study design, intraoperative hemodynamic monitoring, intervention implementation, intraoperative data collection, and manuscript drafting; RHL: Statistical analysis, manuscript revision, and final approval; YCY: Statistical analysis and final manuscript approval; LW: Ethics compliance and postoperative follow-up; XYL: Randomization, blinding, manuscript approval, and publication consent; JHW: Postoperative follow-up data collection and final manuscript approval; DS: Manuscript drafting, critical revision, and final approval.

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Declarations

Competing interests
The authors declare no competing interests.

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