Systematic Review and Meta-Analysis

# Intraoperative goal-directed fluid therapy in adult patients undergoing craniotomies under general anaesthesia: A systematic review and meta-analysis with trial sequential analysis

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## ABSTRACT

**Background and Aims:** Goal-directed fluid therapy (GDFT) has conflicting evidence regarding outcomes in neurosurgical patients. This meta-analysis aimed to compare the effect of GDFT and conventional fluid therapy on various perioperative outcomes in patients undergoing neurosurgical procedures. **Methods:** A comprehensive literature search was conducted using PubMed, EMBASE, Scopus, ProQuest, Web of Science, EBSCOhost, Cochrane and preprint servers. The search was conducted up until 16 October 2023, following PROSPERO registration. The search strategy included terms related to GDFT, neurosurgery and perioperative outcomes. Only randomised controlled trials involving adult humans and comparing GDFT with standard/liberal/traditional/restricted fluid therapy were included. The studies were evaluated for risk of bias (RoB), and pooled estimates of the outcomes were measured in terms of risk ratio (RR) and mean difference (MD). **Results:** No statistically significant difference was observed in neurological outcomes between GDFT and conventional fluid therapy [RR with 95% confidence interval (CI) was 1.10 (0.69, 1.75), two studies, 90 patients, low certainty of evidence using GRADEpro]. GDFT reduced postoperative complications [RR = 0.67 (0.54, 0.82), six studies, 392 participants] and intensive care unit (ICU) and hospital stay [MD (95% CI) were −1.65 (−3.02, −0.28) and −0.94 (−1.47, −0.42), respectively] with high certainty of evidence. The pulmonary complications were significantly lower in the GDFT group [RR (95% CI) = 0.55 (0.38, 0.79), seven studies, 442 patients, high certainty of evidence]. Other outcomes, including total intraoperative fluids administered and blood loss, were comparable in GDFT and conventional therapy groups [MD (95% CI) were −303.87 (−912.56, 304.82) and −14.79 (−49.05, 19.46), respectively]. **Conclusion:** The perioperative GDFT did not influence the neurological outcome. The postoperative complications and hospital and ICU stay were significantly reduced in the GDFT group.

**Keywords:** Craniotomy, fluid therapy, goal-directed, meta-analysis, neurosurgery, neurological outcomes

## INTRODUCTION

Fluid therapy during intraoperative period is vital since significant haemodynamic variations may occur during surgery due to blood loss and fluid shifts.[1] Hypovolemia decreases the perfusion of end organs, such as the



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brain, heart and kidneys, while hypervolemia may lead to congestion and compromise their functioning.[2] In neurosurgical patients, hypovolemia results in cerebral ischaemia, while hypervolemia may cause cerebral oedema.[3,4] Conventionally, intraoperative fluid therapy was managed based on clinical parameters, haemodynamic monitoring including central venous pressure (CVP), and formulas such as Holliday and Segar.[5,6] The role of conventional therapies is being challenged as they fail to detect dynamic circulatory changes.[1] Thus, goal-directed fluid therapy (GDFT) may be required to optimise fluid administration. GDFT refers to the titration of fluids and inotropes according to the predefined haemodynamic goals to maintain adequate organ and tissue perfusion.[7]

In neurosurgical cases, fluid and electrolyte imbalances are commonly seen, and maintaining a tight fluid balance is crucial.[8,9] The literature regarding perioperative GDFT in the neurosurgical population is sparse. A few randomised controlled trials (RCTs) in neurosurgical patients report variable results for neurological outcomes. All existing studies are single-centre studies and they assessed different outcome parameters.

A pooled estimate of the effects of GDFT can help neurosurgeons and anaesthesiologists understand the phenomenon better and assist in clinical decision-making during intraoperative fluid therapy. Hence, this systematic review and meta-analysis (SRMA) of RCTs was planned to compare intraoperative GDFT and conventional fluid therapy in neurosurgical patients undergoing craniotomy for intracranial pathology, with the primary objective of determining the proportion of patients having good neurological outcomes. The secondary outcomes included total fluids administered, blood loss, postoperative complications and intensive care unit (ICU) and hospital length of stay.

## METHODS

The research question of this meta-analysis was 'What is the effect (good or worse) of intraoperative GDFT in adult patients undergoing craniotomies under general anaesthesia on neurological outcomes?' The study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023388850)). The Preferred Reporting Standard of Systematic Reviews and Meta-analysis (PRISMA)[10] guidelines were followed.

### Study design and literature search

Two independent reviewers (KJ and NM) systematically searched the databases, including PubMed, EMBASE, Scopus, ProQuest, Web of Science, EBSCOhost, and Cochrane, on 15 March 2023 for the relevant articles. A top-up search was conducted on 16 October 2023, in which two new studies were found eligible and added. Preprint servers like arXiv, BioRN, ChiRN, ChiRxiv, medRxiv, bioRxiv and SSRN were also searched for relevant articles. The following keywords were used: (neurosurgery, craniotomy, supratentorial, posterior fossa, infratentorial, intracranial aneurysm, traumatic brain injury, head injury); and (goal-directed fluid therapy, goal-oriented fluid therapy, goal-target fluid therapy, restrictive fluid therapy); and [neurological outcome, Glasgow outcome score (GOS), mortality, postoperative complications, cerebral oedema, vasospasm, modified Rankin scale (mRS), kidney injury, hospital duration, total fluid] in both Medical Subject Headings (MeSH) and free terms (title/abstract). The syntaxes used for searching were framed by following the participants, intervention, control and outcome statement [Supplemental Table S1]. The search strategies used in all the included databases are enumerated in Supplemental Table S2. The database output was imported to Mendeley Desktop V1.19.5 software for macOS (Elsevier, Amsterdam, The Netherlands), where duplicate articles were removed.

### Inclusion and exclusion criteria

All RCTs conducted in adult humans undergoing craniotomy for intracranial pathologies comparing GDFT and liberal/traditional/standard fluid management were included. GDFT is defined using an objective physiological parameter to guide fluid therapy intraoperatively with or without inotropes and with or without colloids. The accepted parameters as primary goals are stroke volume variation (SVV), pulse pressure variation (PPV), left ventricular outflow tract velocity–time integral (VTI), cardiac index, stroke volume, cardiac output, pleth variability index (PVI), global end-diastolic volume, and oxygen delivery index. There is no restriction on the type of modality used to achieve GDFT.

The exclusion criteria included animal experiments, retrospective studies, incomplete data for review and quantitative analysis (abstracts only, protocols only, review articles and case reports/series, where elective neurosurgical patients cannot be isolated from conditions like ventriculoperitoneal shunts, or

minor procedures such as burr holes or studies where outcomes are not reported).

### Outcome measures

The primary outcome was to assess the effect of intraoperative GDFT on neurological outcomes as measured by GOS[11] or mRS[12] at discharge.

*Measures of effect:* Neurological outcomes in terms of GOS on a scale of 1–5: lower scores (1–3) were considered as poor and higher scores (4–5) as functionally good, and mRS of 0–3 was a good outcome and 4–6 was a poor outcome. The effect estimate was taken as a risk ratio (RR) with 95% confidence interval (CI). For analysis, we have included the proportion of patients with good neurological outcomes suggested by mRS and GOS.

Secondary outcomes included the following:

1. Postoperative complications [Supplemental Box S1]:
    a. Medical – renal failure, pulmonary complications, cardiac complications, electrolyte abnormalities requiring interventions
    b. Surgical – cerebral oedema, intracranial haematoma, re-exploration surgery, vasospasm, use of radiological interventions
2. Total intraoperative fluid requirements
3. Intraoperative blood loss
4. Duration of hospital (total days in hospital)/ ICU stay (defined as from the day of surgery to discharge from ICU).
5. Mortality.

Postoperative complications and mortality within the same hospital admission or till the patient is discharged or death happens were measured as a ratio with 95% CI**.** Duration of hospital/ICU stay, blood loss and total fluid infused were measured as mean differences (MDs).

Data on study characteristics like authors, year, place, intervention/control and outcomes, and demographic characteristics were extracted. Other disease and patient characteristics were extracted.

### Study evaluation and selection

#### *Screening of title abstracts*

Two independent reviewers (KJ and NM) reviewed the articles' title abstracts derived from the systematic search for suitability for a full-text review. Any discrepancies regarding the article's suitability were resolved by a third independent reviewer (APG).

#### *Full-text screening and extraction of data*

Studies found suitable for full-text review were evaluated independently by two reviewers (KJ and NM) based on the eligibility criteria, and data extraction was done subsequently. Any discrepancies regarding the article's eligibility for data extraction were settled by the third reviewer (APG). A data extraction table was formulated in a Microsoft Excel sheet to facilitate the analysis.

### Risk-of-bias (quality) assessment

The studies were evaluated for risk of bias (RoB) by independent assessors (KJ, MAS and NM) using the RoB2 tool from the Cochrane Collaboration (London, UK).[13] We analysed the bias in the following domains: 'randomisation, deviations from intended intervention, missing outcome data, outcome measurement and selection of reported result'. In case of disagreements, the discrepancies were settled by discussion among all the reviewers (KJ, NM, AGP, MAS and BKP). Each domain's RoB was categorised as either low, with some concerns, or high. RoB is represented (Robvis in R software, Version 4.3.1 for Mac; RStudio, Boston, MA, USA) at each study's outcome level and is presented alongside the study estimates in the respective forest plots.

### Data analysis

The pooled estimates of the outcomes, along with a 95% CI, were measured in terms of RR and MD, depending on the outcomes. The median and interquartile range parameters were converted to mean and standard deviation for analysis using an online converter.[14] The heterogeneity of studies was assessed using the $I^2$ test. If $P > 0.05$ for the Q test or $I^2 < 50\%$, the fixed effects model (the Mantel Haenszel method)[15] was used to estimate RR. If $I^2 > 50\%$, a random effects model was planned. The prediction interval (PI) was calculated based on the $Tau^2$ statistics.[16] Assessment of publication bias was planned by using the funnel plot and Egger's test if more than ten studies were found eligible for meta-analysis and the doi plot if more than five studies were found eligible. A trim-and-fill method was also planned if publication bias was identified. A sensitivity analysis was planned after removing the studies of high RoB and using a leave-one-out meta-analysis. A post hoc trial sequential analysis

was done for the seven critical outcomes, and it was finally used to assess evidence certainty. A *P* value of <0.05 was deemed to be significant. All analyses were undertaken using R Studio software following the standard code.[17]

### *Certainty in the evidence*

The study evaluated and summarised the pooled estimate's certainty for each outcome with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) methodology[18] using the GRADEpro software.

## RESULTS

### Study selection

The sequential process of study selection and review, as per the PRISMA flow chart for reporting systematic reviews, is depicted in Figure 1. A total of 125 articles were identified after a comprehensive search of the Cochrane ($n$ = 39), EBSCOhost ($n$ = 23), EMBASE ($n$ = 21), ProQuest ($n$ = 6), PubMed ($n$ = 5), Scopus ($n$ = 17) and Web of Science ($n$ = 14). After removing the duplicates using Mendeley, 78 articles were screened for title and abstract. After reviewing the title abstract, 16 articles were screened for full-text reading. Of these, seven articles did not meet the inclusion criteria. The bibliography screening and grey literature search provided one more article. Finally, ten studies were included for SRMA.[19-28]

### Study characteristics

The individual study demographics are presented in Table 1. A total of 608 patients were included for analysis, with 309 and 299 patients in the experimental (E) and control (C) groups, respectively, and with sample sizes ranging from 10 to 72 in the control group and 16 to 73 patients in the experimental group. Five studies were conducted in patients with intracranial tumours, one in intracranial aneurysms and four in all craniotomies (brain abscess, aneurysms, tumours). The patients' mean age in the experimental group varied from 41 to 61 years, while 39 to 58.4 years in the control group.

### Outcomes of pooled studies

***a. Primary outcomes:***

*Neurological outcomes:* Only two RCTs reported neurological outcomes measured by GOS and mRS at discharge.[19,21] The proportion of patients with favourable outcomes was extracted from the studies. The pooled estimate did not show a significant difference in favourable neurological outcomes between the GDFT and control groups [RR (95% CI) = 1.10 (0.69–1.75), $I^2$ = 74%] [Figure 2a].

***b. Secondary outcomes:***

*Postoperative complications:* Six of the included RCTs reported the incidence of overall postoperative complications.[19,22,24-26,28] The pooled estimate revealed that GDFT patients had a significantly lower risk of

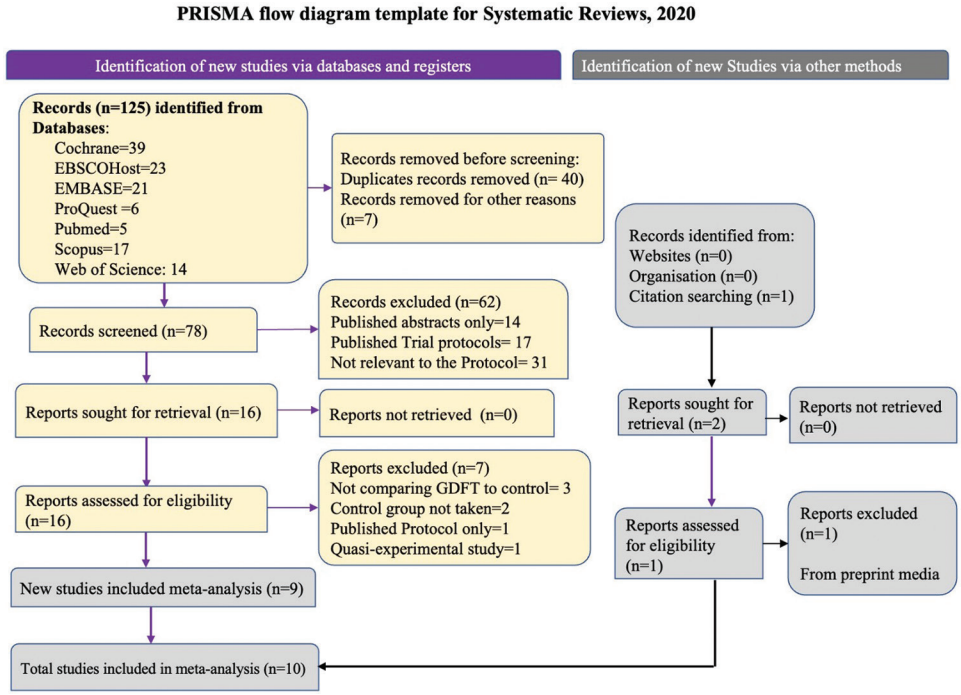


**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart

**Table 1: Characteristics of included studies (*n*=10)**

| Author, year | Country | Study design | Population | GDFT technique | Number of patients | | Male/female | | Age Mean (SD) | | Outcomes reported |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | C | E | C | E | C | E | |
| Feng *et al*.[24] 2023 | China | RCT | Meningioma resection | LiDCO rapid system, SVV <13%, ΔSV 10% | 42 | 42 | 13/29 | 13/29 | 53 (12) | 54 (9) | Composite complication<br>Rate in terms of Clavin Dindo grade, intraoperative haemodynamics and fluids, postoperative complications, encephaledema, GI function recovery, ICU and hospital stay and mortality |
| Hrdy *et al*.[25] (2023) | Brno, Czech Republic | RCT | Elective neurosurgical patients | Starling SV monitor, CI <2.5, SVV <15% | 17 | 17 | 5/12 | 2/15 | 58.4 (9.5) | 56.9 (16.8) | BRS at the end of surgery and brain oedema requiring therapy, total crystalloids, colloids, transfusions and blood loss, hypotensive episodes (MAP <65 Torr), vasoactive drug intervention, urine output till 24 h postoperatively, blood transfused, postoperative complications, duration of ICU and hospital stay and 28-day mortality |
| Bloria *et al*.[21] (2022) | India | RCT | Intracranial aneurysms clipping | TEE measured LVOT-VTI <15 cm, variation <12% | 25 | 25 | 8/17 | 9/16 | 53.8 (11.9) | 50.9 (7.7) | Haemodynamic parameters, intraoperative blood loss, urine output, lactate, postoperative creatinine, duration of mechanical ventilation, length of stay in ICU and hospital, mRS at discharge and GOS-E at 6 months |
| Mishra *et al*.[19] (2022) | India | RCT | Large supratentorial tumours | Flotrac Vigileo, CI >2.5 and SVV <12% | 20 | 20 | 11/9 | 14/6 | 39 (11) | 44 (12.6) | Duration of hospital stay and ICU stay, neurological outcomes, incidence of tight brain, intraoperative blood loss and total amount of fluids, intraoperative and postoperative complications |
| Mitrev *et al*.[26] (2019) | USA | RCT | Elective craniotomy | Flotrac Vigileo, CI >2.5 and SVV <15% | 10 | 16 | 7/3 | 8/8 | 56 | 55 | Intraoperative fluid administered, blood loss, haemodynamics, phenylephrine and ephedrine, serum lactate levels, MAP, ICU and hospital length of hospital stay, neurological and non-neurological complications |
| Kim *et al*.[27] (2019) | Korea | RCT | Elective craniotomy | Flotrac Vigileo monitor, SVV <13% | 24 | 24 | 7/17 | 9/15 | 51.3 (13) | 48.6 (14) | Intraoperative fluid administered, phenylephrine and ephedrine, haemodynamic parameters, acid–base parameters, blood loss |
| Hassanin *et al*.[23] (2019) | Egypt | RCT | Supratentorial tumours | (GE solar 8000M/I monitor), PPV <13% | 30 | 31 | 12/18 | 16/15 | 39 (13) | 41 (12) | Brain relaxation scores, haemodynamic parameters, intraoperative fluid and length of hospital stay |
| Luo *et al*.[22] (2017) | China | RCT | Brain tumours, abscess, aneurysms | Flotrac Vigileo, CI <2.5 and SVV <15 | 72 | 73 | 32/40 | 30/43 | 62 (13) | 61 (13) | Amount of crystalloids and colloids, postoperative complications, duration of ICU stay and hospital stay, costs and 30-day mortality |
| Sundaram *et al*.[20] (2016) | India | RCT | Supra- and infratentorial tumours | Philips Intellivue MP50 monitor, PPV <13% | 29 | 28 | 12/17 | 11/17 | 43.4 (10.3) | 39.9 (13.9) | Intraoperative haemodynamic parameters, intraoperative blood loss and amount of intravenous fluids |
| Wu *et al*.[28] (2016) | China | RCT | Supratentorial tumours | Flotrac Vigileo, SVV <12% | 30 | 33 | 14/16 | 15/18 | 50 (9) | 50 (9) | Amount of intraoperative and postoperative fluids, haemodynamic parameters, degree of brain oedema, length of ICU and hospital stay, postoperative complications, biochemical parameters |

BRS=brain relaxation score, C=control, CI=Cardiac Index, E=experimental, GDFT=goal-directed fluid therapy, GI=gastrointestinal, GOS-E=extended Glasgow outcome score, ICU=intensive care unit, LiDCO=lithium dilution cardiac output, LVOT-VTI=left ventricular outflow tract velocity–time integral, MAP=mean arterial pressure, mRS=modified Rankin score, PPV=pulse pressure variations, RCT=randomised controlled trial, SD=standard deviation, , SV=stroke volume, SVV=systolic volume variations, TEE=transoesophageal echocardiography

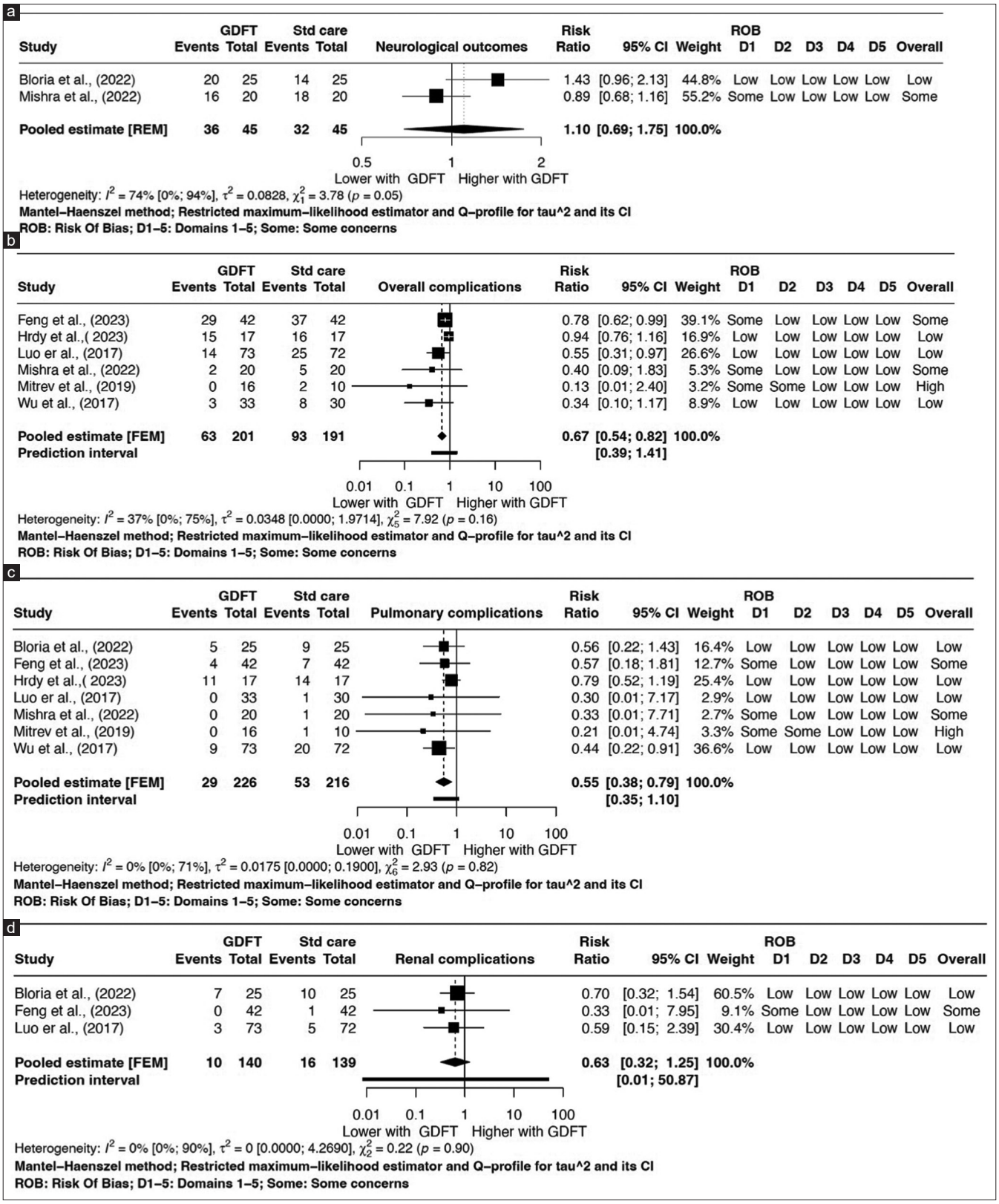


**Figure 2:** Forest plots of outcomes represented as proportions: (a) neurological outcomes, (b) postoperative complications, (c) pulmonary complications, and (d) renal complications. CI = confidence interval, FEM = fixed effects model; GDFT = goal-directed fluid therapy, REM = random effects model, RoB = risk of bias, Std = standard care

postoperative complications than the control group [RR (95% CI) = 0.67 (0.54, 0.82), 95% PI = 0.39, 1.41, $I^2$ = 37%] [Figure 2b]. Pulmonary complications were reported in seven studies.[19,21,22,24-26,28] The pooled

estimate showed a significant reduction in pulmonary complications with the use of GDFT compared to the control group [RR (95% CI) = 0.55 (0.38, 0.79), 95% PI = 0.35, 1.10, $I^2$ = 0%] [Figure 2c]. Renal complications were reported in three studies.[21,22,24] However, no significant difference was seen in the incidence of postoperative kidney injury with the use of GDFT compared to the control group [RR (95% CI) = 0.63 (0.32, 1.25), 95% PI = 0.01, 50.87, $I^2$ = 0%] [Figure 2d].

*Total amounts of fluids:* Six RCTs reported the total amount of intravenous fluids used perioperatively.[19,21,23,24,26,28] The pooled MD did not show a significant difference in the volume of fluids used between the GDFT and control groups intraoperatively [MD (95% CI) = −303.87 (−912.56, 304.82), 95% PI = −2397.76, 1790.02, $I^2$ = 94%] [Figure 3a]. The pooled estimate for average total fluids remained consistent with the exclusion of any study except Bloria *et al*.[21] Excluding this study led to statistical significance.

*Amount of intraoperative blood loss:* Mean blood loss was reported by eight RCTs included in this meta-analysis.[19–24,27,28] The pooled MD did not show a significant difference in intraoperative blood loss between the GDFT and control groups [MD (95% CI) = −14.79 (−49.05, 19.46), 95% PI = −66.82, 38.38, $I^2$ = 33%] [Figure 3b].

*Duration of ICU and hospital stay:* A total of six RCTs reported the duration of ICU stay,[19,21-23,25,28] and eight studies reported the duration of hospital stay.[19,21-26,28] Patients in the GDFT group had significantly shorter ICU stays than the patients in the control group [MD (95% CI) = −1.6 (−3.02, −0.28)]. The PI ranged from − 5.63 to 2.33 [Figure 3c]. Moderate heterogeneity was found between the studies for the duration of ICU stay ($I^2$ = 77%, $P$ = 0.01). The pooled estimate for average ICU stay remained fairly consistent, excluding any study except Luo *et al*.[22] Excluding this study led to statistical insignificance. The pooled MD showed a significant difference in the overall duration of hospital stay favouring GDFT [MD (95% CI) = −0.97 (−1.5, −0.4), 95% PI − 3.17, 0.64, $I^2$ = 41%] [Figure 3d].

### RoB assessment

RoB assessed by the independent reviewers (NM, KJ, MAS) is shown in Figure 4. Three of the studies have some concerns due to bias arising from allocation concealment[19,24] and measurement of outcomes,[20] and two studies had an overall high RoB arising due to some concerns in allocation concealment and deviations from assigned interventions.[27,28] All other studies had a generally low RoB, with none displaying a high RoB either overall or in any of the domains.

### Sensitivity analysis

Sensitivity analysis was conducted for the outcome where the studies with high RoB were included in the pooled estimate. The neurological outcome was not affected by considering only the studies with low RoB [RR (95% CI) = 1.43 (0.96, 2.13)] [Figure 5]. The sensitivity analysis for overall and pulmonary complications also showed a similar effect, omitting studies with high RoB [Figure 5, Figure 1S]. The direction of the total fluid pooled estimate was similar for both high- and low-RoB studies, but omitting Bloria *et al*.[21] caused a significant change in the pooled estimate [Figure 6, Figure 2S]. This may be due to the use of different fluid management algorithms. The pooled estimate for the duration of hospital stay showed similar results when considering only low-risk bias studies groups [MD (95% CI) = −0.70 (-1.33, -0.07)] compared to the earlier overall estimate groups [MD (95% CI) = −0.94 (−1.47, -0.42)] [Figure 6]. Omitting any study does not change the direction of the effect [Figure 2S].

### Trial sequential analysis

A trial sequential analysis was done *post hoc* and showed that the required sample size was met for blood loss, hospital stay, and ICU stay. However, a much greater sample size is needed for pulmonary and renal complications [Table S3]. The software could not compute this for neurological outcomes and overall complications due to small number of studies.

### GRADE profile

There was high certainty of evidence for overall complications, pulmonary complications and hospital and ICU stay. The other outcomes showed a low to very low certainty of evidence [Table 2].

## DISCUSSION

The present comprehensive meta-analysis revealed no significant effect of GDFT on neurological outcomes. However, postoperative complications were significantly lower, and the hospital and ICU stay duration was significantly less in the GDFT group. Other outcome parameters were comparable among the groups.

There are a few studies where GDFT was used in the ICU or the postoperative period. Anetsberger *et al*.[29]

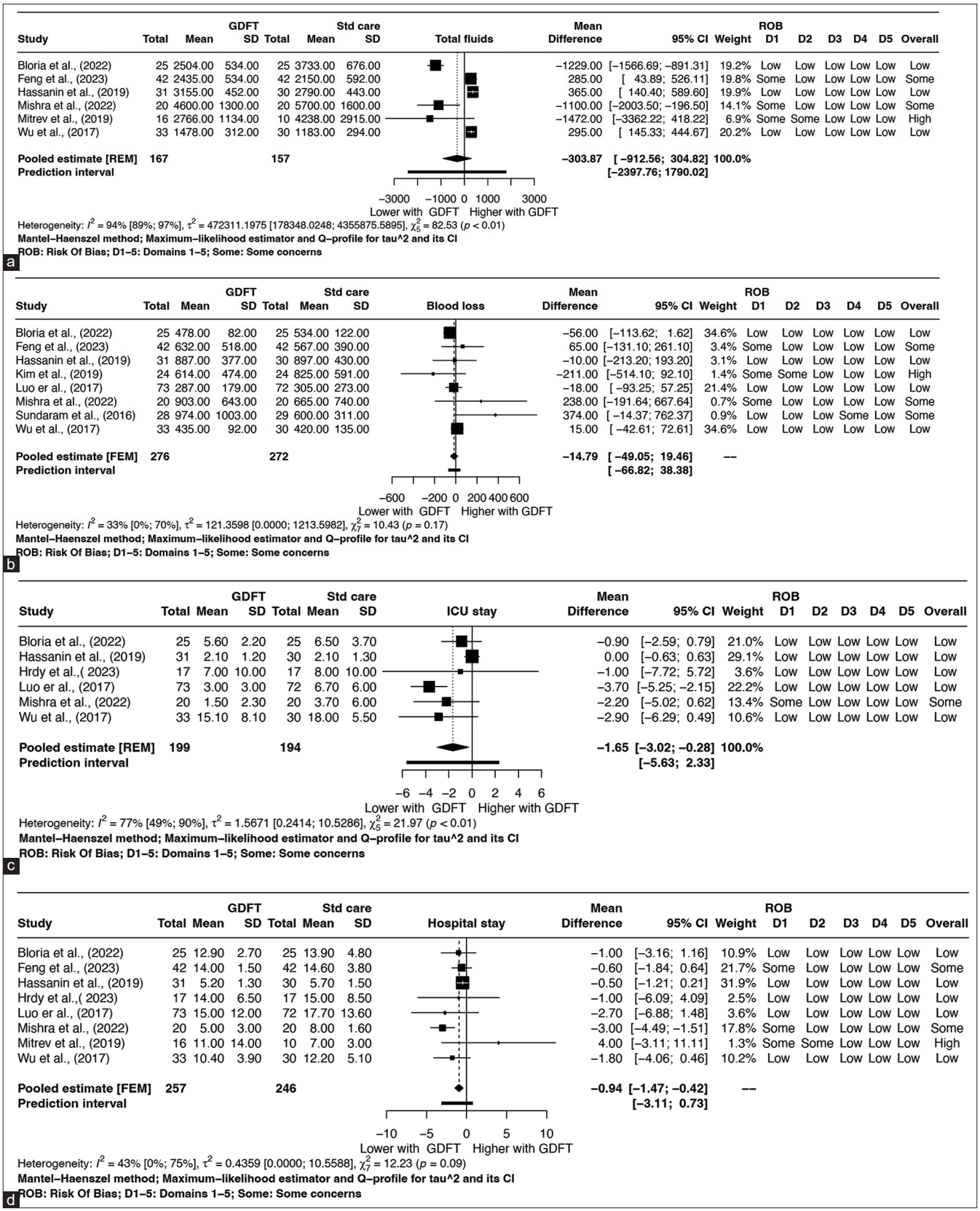


**Figure 3:** Forest plots of outcomes reported as mean differences: (a) total amount of the fluid; (b) total amount of intraoperative blood loss; (c) duration of ICU stay; (d) duration of hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, REM = random effects model, RoB = risk of bias, SD = standard deviation, Std = standard

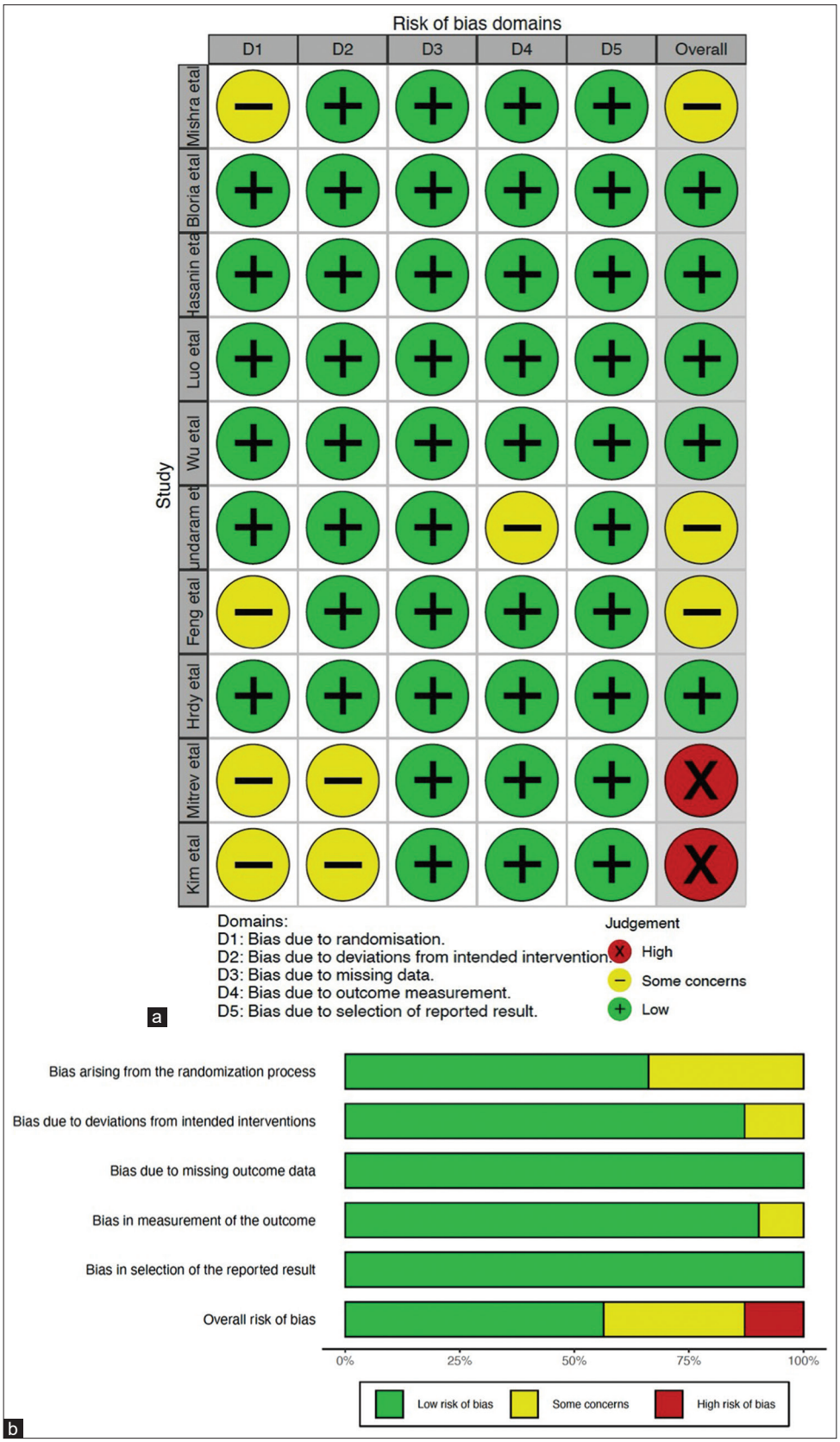


**Figure 4:** Risk of bias summary for individual study: (a) using traffic signal light plot designed via Robvis tool; (b) using weighted plot designed via RoB tool. All studies were given equal weight for qualitative assessment

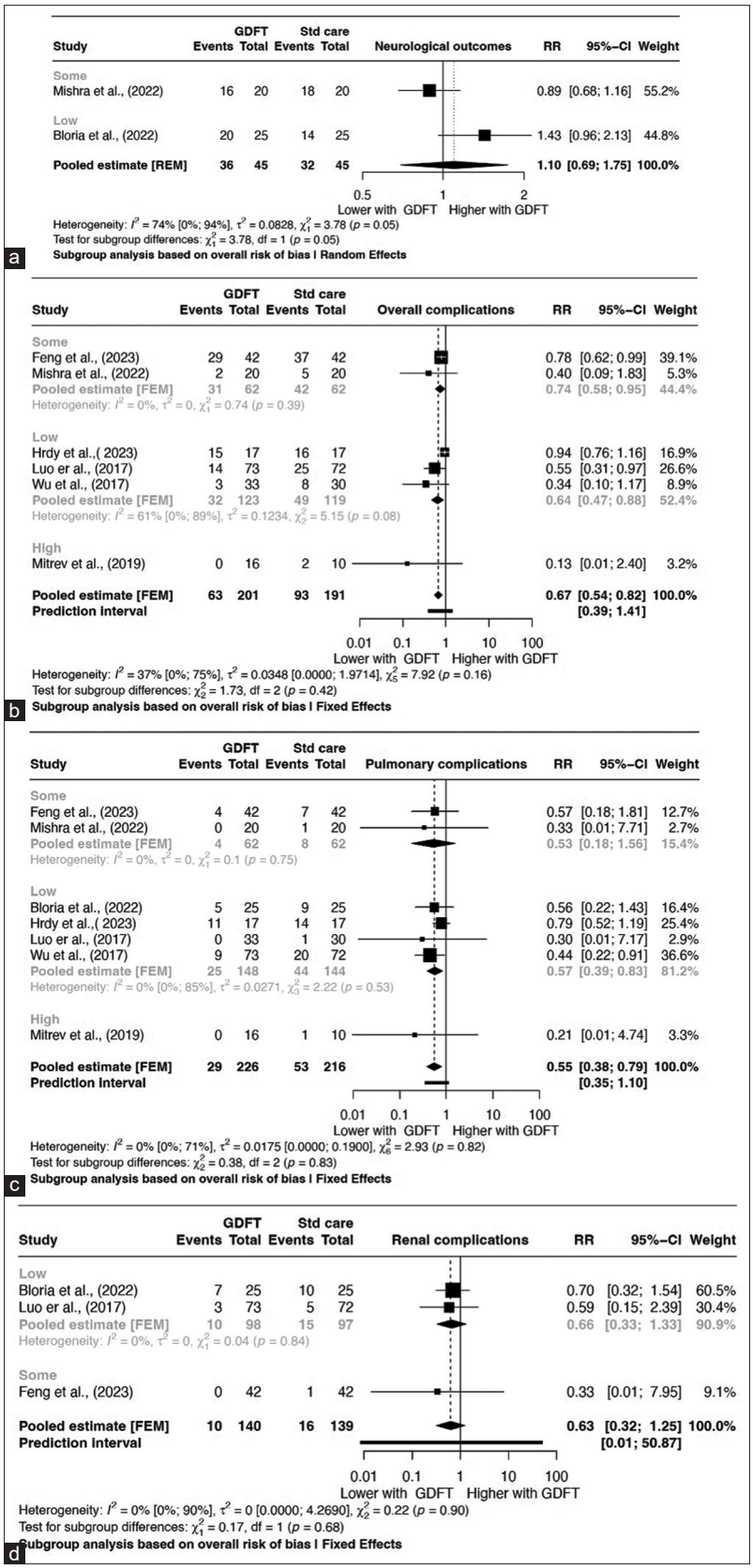


**Figure 5:** Sensitivity analysis of the proportion data: (a) neurological outcomes, (b) overall complications, (c) pulmonary complications and (d) renal complications. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, REM = random effects model, RR = risk ratio, Std = standard care

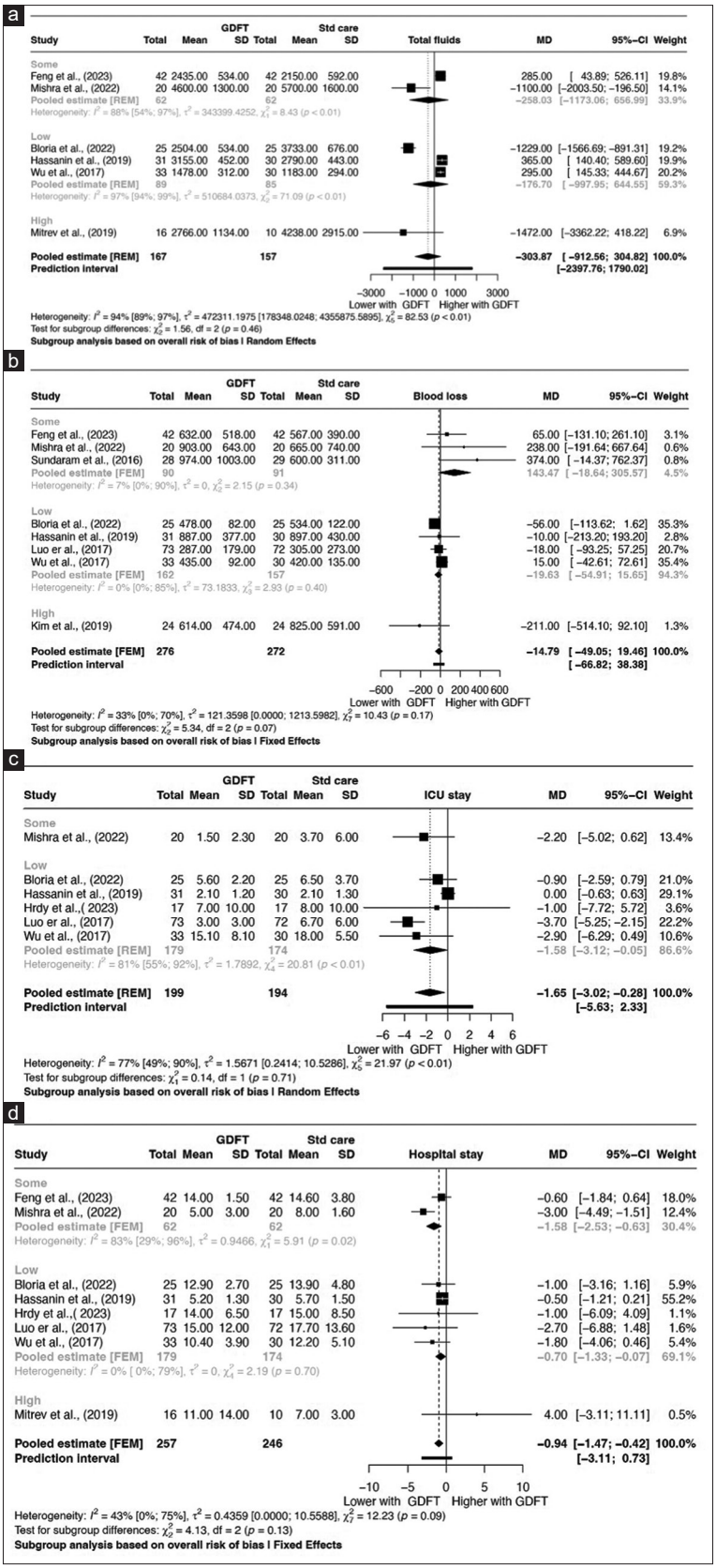


**Figure 6:** Sensitivity analysis of the data with mean difference: (a) total fluids; (b) blood loss; (c) ICU stay and (d) hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, ICU = intensive care unit, MD = mean difference, REM = random effects model, SD = Standard deviation, Std = standard care

**Table 2: Certainty of evidence as generated by GRADEpro software**

**GDFT compared to standard therapy in adult patients undergoing craniotomies**

Patient or population: Adult patients undergoing craniotomies
Intervention: Goal-directed fluid therapy (GDFT)
Comparison: Standard therapy

| Outcomes | No. of participants (studies) Follow-up | Certainty of the evidence (GRADE) | Relative effect (95% CI) | Anticipated absolute effects | |
|---|---|---|---|---|---|
| | | | | Risk with standard therapy | Risk difference with GDFT |
| Neurological outcomes | 90 (2 RCTs) | ⊕◯◯◯ Very low[a,b] | RR 1.10 (0.69-1.75) | 711 per 1,000 | 71 more per 1,000 (220 fewer to 533 more) |
| Overall complications | 392 (6 RCTs) | ⊕⊕⊕⊕ High | RR 0.67 (0.54-0.82) | 487 per 1,000 | 161 fewer per 1,000 (224 fewer to 88 fewer) |
| Pulmonary complications | 442 (7 RCTs) | ⊕⊕⊕⊕ High | RR 0.55 (0.38-0.79) | 245 per 1,000 | 110 fewer per 1,000 (152 fewer to 52 fewer) |
| Renal complications | 279 (3 RCTs) | ⊕⊕◯◯ Low[c] | RR 0.63 (0.32-1.35) | 115 per 1,000 | 43 fewer per 1,000 (78 fewer to 40 more) |
| Total fluids | 324 (6 RCTs) | ⊕◯◯◯ Very low[a,c] | - | The mean total fluids ranged from 1183 to 5700 ml | MD 303.87 ml lower (912.56 lower to 304.82 higher) |
| Hospital stay | 503 (8 RCTs) | ⊕⊕⊕⊕ High | - | The mean hospital stay ranged from 5.7 to 17.70 days | MD 0.94 days higher (1.47 lower to 0.42 lower) |
| ICU stay | 393 (6 RCTs) | ⊕⊕⊕⊕ High | - | The mean ICU stay ranged from 2.1 to 18 days | MD 1.65 days lower (3.02 lower to 0.28 lower) |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; MD: Mean difference; RR: Risk ratio. GRADE Working Group grades of evidence, ICU: Intensive care unit; RCT: Randomised controlled trial. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. [a]Point estimates are present on both the sides of line of no effect, hence we have downgraded evidence certainty by one level, [b]The point estimate suggests harm, and the CI includes the possibility of important benefit, hence we have downgraded the evidence certainty by two levels. [c]The point estimate suggests benefit, and the CI includes the possibility of important harm, hence we have downgraded the evidence certainty by two levels

compared GDFT with standard therapy throughout the hospital stay in patients with aneurysmal subarachnoid haemorrhage (SAH) and observed that the GDFT group had a significantly lesser incidence of delayed cerebral ischaemia and better neurological outcome (GOS 5) at 3 months following discharge. Mutoh *et al*.[30] observed similar results when comparing GDFT with conventional treatment in post-clipping or post-coiling poor-grade patients. Hence, it is suggested that GDFT should be continued till the patient needs systemic fluid administration in future studies. This may enable us to appreciate its effect on neurological outcomes better.

The pooled data has shown that the number of postoperative complications was significantly lower in the GDFT group. Similar observations were made in various high-risk non-neurosurgical patients as well.[31-33] A meta-analysis conducted in major gastrointestinal and non-cardiac surgeries showed a reduction in the major postoperative complications in the GDFT group.[34] In contrast, a multicentric retrospective analysis of a before–after study conducted in neurosurgical patients showed that GDFT did not reduce the major postoperative complications in elective neurosurgical patients.[35] In the present meta-analysis, there was a lot of heterogeneity in reporting other medical and surgical complications. Only pulmonary and renal complications could be analysed separately. Intraoperative GDFT may reduce postoperative complications due to better systolic blood pressure maintenance and optimum volume without over- or underhydration. The overall certainty of evidence about this outcome was high.

The pooled data showed that the total amount of intraoperative fluid was similar in both groups. The studies included in this meta-analysis have used different algorithms and various tools to guide fluid therapy, including SVV (>12%[19,27] and >15%),[22] PPV (>13%)[20,23] and VTI (>12%),[21] and various protocols of type of fluids. A study by Dey *et al*.[36] compared SVV with PVI and found that the amount of crystalloids was significantly different in these techniques of GDFT. Wu *et al*.[37] Compared with a low SVV of 10% to a high SVV of 18%, it was found that lower SVV was superior in terms of shorter ICU stay, postoperative neurological events, serum lactate, and Barthel index at discharge. Hence, high heterogeneity was observed for this outcome, and it is suggested that larger multicentric trials with uniform targets and algorithms be included to reach a firm conclusion on this outcome.

Intraoperative blood loss was comparable among the groups. Even though a previous study in major hepatectomy showed that blood loss was significantly lesser in the GDFT group (SVV guided) compared to the control group (CVP guided),[38] most of the studies in neurosurgical patients failed to show the direct benefit of GDFT in reducing blood loss. A lesser amount of blood loss was observed during hepatectomy due to the favourable effect of GDFT on haemodynamic parameters. In neurosurgical procedures, intraoperative blood loss primarily depends upon vascularity, size and location of the lesions, technical difficulties and surgical expertise.[39] GDFT may not directly influence the blood loss as it does in hepatectomy.

The duration of ICU and hospital days was significantly less in the GDFT group. The reduction in postoperative complications may explain the lesser duration of ICU and hospital stay in the GDFT group. A previous meta-analysis conducted in major abdominal surgeries showed that hospital length of stay was significantly lesser in the GDFT group. Similarly, Benes *et al*.[32] reported significantly fewer days of ICU stay in surgical patients in a heterogeneous population. This may, in turn, improve patient-reported outcomes such as the cost of care. This outcome has a high certainty of evidence.

### Strength and limitations

This is the first comprehensive SRMA conducted to examine the effect of GDFT on multiple outcomes in neurosurgical patients. The major limitation was the smaller number of high-quality studies to assess the role of GDFT in neurosurgical patients. The composition of fluids governing the osmolarity and solute content also affects the outcome. In the current meta-analysis, the studies have used different types of fluids, including balanced crystalloids, normal saline and colloids. Hence, there is a heterogeneity in the type of fluid infused, the fluid protocol followed, the technique of GDFT and the outcome studied. The certainty of evidence was of low grade for the primary outcome parameter. Furthermore, large multicentric RCTs with uniform techniques and tools to measure the targets of GDFT and outcomes are required to understand the effect of GDFT among neurosurgical patients.

## CONCLUSIONS

The pooled data of this meta-analysis showed that the neurological outcome was not affected by the intraoperative GDFT. Still, it was associated with reduced postoperative complications and ICU and hospital stays, reducing the overall cost.

### Authors' contribution

Authors KJ and APG contributed equally as the first authors. All the authors have participated sufficiently in the work to merit authorship and publicly defend the manuscript contents.

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### Conflicts of interest

There are no conflicts of interest.

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## LIST OF SUPPLEMENTAL DIGITAL CONTENT

### Supplemental digital content 1

| Box 1: Definitions for secondary outcomes |
|---|
| 1. Renal failure: Increased creatinine >1.5 times from baseline, decreased urine out put <0.5 ml/kg, acute kidney injury |
| 2. Pulmonary complication: Pneumonitis, pleural effusion, pulmonary thromboembolism, consolidation |
| 3. Cardiac complication: hypotension and arrhythmias requiring intervention |
| 4. Electrolyte abnormalities requiring treatment |
| 5. Re-exploration: Redo surgery during same hospital admission |

## Supplemental digital content 2

| Supplemental Table S1: PICO statement of the study | | |
|---|---|---|
| | **Inclusion** | **Exclusion** |
| Participants | Patients undergoing craniotomies for neurosurgical conditions<br>• All genders<br>• Adults | Emergency room resuscitation<br>Emergency surgical procedure |
| Intervention | Goal-directed fluid therapy | |
| Outcome | • Postoperative complications<br>• Mortality | |
| Study designs | Randomised controlled trials<br>Geography- global level<br>Date of Search- published till 16 October 2023<br>English language<br>Human studies<br>Published and unpublished data | Retrospective, case reports and opinion reports |

PICO=Participants, intervention, control and outcome

## Supplemental digital content 3

| Supplemental Table S2: The search strategies and results of various databases included (as of 16.10.2023) | | | |
|---|---|---|---|
| **Database** | **No.** | **Search query** | **Results** |
| | | **Cochrane** | |
| | #1 | (((((Neurosurgery: ti, ab)) OR (Craniotomy: ti, ab)) OR (Supratentorial: ti, ab)) OR (Posterior fossa: ti, ab) OR (Infratentorial: ti, ab) OR (Intracranial aneurysm: ti, ab) OR (Traumatic brain injury: ti, ab) OR (Head Injury: ti, ab)) | 11,387 |
| | #2 | (((((goal directed fluid therapy: ti, ab)) OR (goal oriented fluid therapy: ti, ab)) OR (goal target fluid therapy: ti, ab)) OR (restrictive fluid therapy: ti, ab)) | 890 |
| | #3 | ((((((((((neurological outcome: ti, ab)) OR (Glasgow outcome score: ti, ab)) OR (Mortality: ti, ab)) OR (postoperative complications: ti, ab)) OR (cerebral edema: ti, ab)) OR (vasospasm: ti, ab)) OR (Modified Rankin scale: ti, ab)) OR (Kidney injury: ti, ab)) OR (Hospital duration: ti, ab)) OR (Total fluid: ti, ab)) | 174,556 |
| | #4 | #1 AND #2 AND #3 AND (English) | 39 |
| | | **EBSCOhost-academic search complete** | |
| | #1 | TX neurosurgery OR TX craniotomy OR TX supratentorial OR TX posterior fossa OR TX Infratentorial OR TX Intracranial aneurysm OR TX traumatic brain injury OR TX head Injury | 138,431 |
| | #2 | TX goal-directed fluid therapy OR TX goal-oriented fluid therapy OR TX goal-target fluid therapy OR TX restrictive fluid therapy | 281 |
| | #3 | TX neurological outcome OR TX Glasgow outcome score OR TX mortality OR TX postoperative complications OR TX cerebral edema OR TX vasospasm OR TX modified Rankin scale OR TX Kidney injury OR TX Hospital duration OR TX Total fluid | 672,597 |
| | #4 | 1 AND #2 AND #3 AND (English[Filter]) | 23 |
| | | **EMBASE** | |
| | #1 | (neurosurgery: ti, ab OR craniotomy: ti, ab OR supratentorial: ti, ab OR (posterior AND fossa: ti, ab) OR infratentorial: ti, ab OR (intracranial AND aneurysm: ti, ab) OR (traumatic AND ('brain'/exp OR brain) AND injury: ti, ab) OR (('head'/exp OR head) AND injury: ti, ab)) AND [english]/lim | 224,839 |
| | #2 | (((((goal directed fluid therapy: ti, ab)) OR (goal oriented fluid therapy: ti, ab)) OR (goal target fluid therapy: ti, ab)) OR (restrictive fluid therapy: ti, ab)) AND [english]/lim | 2105 |
| | #3 | ((((((((((neurological outcome: ti, ab)) OR (glasgow outcome score: ti, ab)) OR (mortality: ti, ab)) OR (postoperative complications: ti, ab)) OR (cerebral edema: ti, ab)) OR (vasospasm: ti, ab)) OR (modified rankin scale: ti, ab)) (Kidney injury: ti, ab)) OR (Hospital duration: ti, ab)) OR (Total fluid: ti, ab)) AND [english]/lim | 550,892 |
| | #4 | #1 AND #2 AND #3 AND | 21 |
| | | **ProQuest** | |
| | #1 | ((TI, AB (neurosurgery)) OR (TI, AB (craniotomy))) OR (TI, AB (supratentorial)) OR (TI, AB (posterior fossa)) OR (TI, AB (infratentorial)) OR (TI, AB (intracranial aneurysm)) OR (TI, AB (traumatic brain injury)) OR (TI, AB (head Injury)) | 22,986 |
| | #2 | (((TI, AB (goal directed fluid therapy)) OR (TI, AB (goal oriented fluid therapy))) OR (TI, AB (goal target fluid therapy))) OR (TI, AB (restrictive fluid therapy)) | 280 |
| | #3 | ((((TI, AB (neurological outcome)) OR (TI, AB (Glasgow outcome score))) OR (TI, AB (Mortality))) OR ((((TI, AB (postoperative complications)) OR (TI, AB (cerebral edema))) OR (TI, AB (vasospasm))) OR (TI, AB (Modified Rankin scale))) OR (TI, AB (kidney injury))) OR ((TI, AB (Hospital duration))) OR (TI, AB (total fluid)) | 275,195 |
| | #4 | 1 AND 2 AND 3 AND (English[Filter] ) | 6 |
| | | **PubMed** | |
| | #1 | (((((((Neurosurgery[Title/Abstract]) OR (Craniotomy[Title/Abstract])) OR (Supratentorial[Title/Abstract])) OR (Posterior fossa[Title/Abstract])) OR (Infratentorial[Title/Abstract])) OR (Intracranial aneurysm[Title/Abstract])) OR ('Traumatic brain injury'[Title/Abstract])) OR ('Head Injury'[Title/Abstract]) | 13,421 |
| | #2 | (((goal-directed fluid therapy[Title/Abstract]) OR (goal-oriented fluid therapy[Title/Abstract])) OR (goal-target fluid therapy[Title/Abstract])) OR (Restrictive fluid therapy[Title/Abstract]) | 436 |
| | #3 | (((((((((neurological outcome[Title/Abstract]) OR (Glasgow outcome scales[Title/Abstract])) OR (Modified Rankin scale[Title/Abstract])) OR (Mortality[Title/Abstract])) OR (postoperative complications[Title/Abstract])) OR (Kidney injury[Title/Abstract])) OR (cerebral edema[Title/Abstract])) OR (vasospasm[Title/Abstract])) OR (Hospital duration[Title/Abstract])) OR (Total fluid[Title/Abstract]) | 1,125,206 |
| | #4 | #1 AND #2 AND #3 AND (English[Filter]) | 5 |
| | | **Scopus** | |
| | #1 | ( TITLE-ABS ( neurosurgery ) ) OR ( TITLE-ABS ( craniotomy ) ) OR ( TITLE-ABS ( supratentorial ) ) OR ( TITLE-ABS ( posteriorAND fossa ) ) OR ( TITLE-ABS ( infratentorial ) ) OR ( TITLE-ABS ( intracranial AND aneurysm ) ) OR ( TITLE-ABS ( traumatic AND brain AND injury ) ) OR ( TITLE-ABS ( head AND injury ) ) | 204,602 |
| | #2 | ( ( TITLE-ABS ( goal-directed fluid therapy ) ) OR ( TITLE-ABS ( goal-oriented fluid therapy ) ) ) OR ( TITLE-ABS ( goal target fluid therapy ) ) OR ( TITLE-ABS ( restrictive fluid therapy ) ) | 1402 |

*Contd...*

| Supplemental Table S2: Contd... | | | |
|---|---|---|---|
| **Database** | **No.** | **Search query** | **Results** |
| | | **Scopus** | |
| | #3 | ( TITLE-ABS ( neurological outcome ) ) OR ( TITLE-ABS (Glasgow outcome score ) ) OR ( TITLE-ABS ( Mortality ) ) OR ( TITLE-ABS ( kidney injury ) ) OR ( TITLE-ABS ( hospital duration ) ) OR ( TITLE-ABS ( postoperative complications ) ) OR ( TITLE-ABS ( cerebral oedema) ) OR ( TITLE-ABS ( vasospasm ) ) OR ( TITLE-ABS ( Modified Rankin scale ) ) OR ( TITLE-ABS ( Total fluid ) ) | 1,766,902 |
| | #4 | #1 AND #2 AND #3 AND (English[Filter]) | 17 |
| | | **Web of Science** | |
| | #1 | (TI=neurosurgery OR AB=neurosurgery) OR (TI=craniotomy OR AB=craniotomy) OR (TI=supratentorial OR AB=supratentorial) OR (TI=posterior fossa OR AB=posterior fossa) OR (TI=infratentorial OR AB=infratentorial) OR (TI=intracranial aneurysm OR AB=intracranial aneurysm) OR (TI=traumatic brain injury OR AB=traumatic brain injury) OR (TI=head Injury OR AB=head Injury) | 142,856 |
| | #2 | (TI=goal-directed fluid therapy OR AB=goal-directed fluid therapy) OR (TI=goal-oriented fluid therapy OR AB=goal-oriented fluid therapy) OR (TI=goal target fluid therapy OR AB=goal target fluid therapy) OR (TI=restrictive fluid therapy OR AB=restrictive fluid therapy) | 1062 |
| | #3 | (TI=neurological outcome OR AB=neurological outcome) OR (TI=Glasgow outcome score OR AB=Glasgow outcome score) OR (TI=Mortality OR AB=Mortality) OR (TI=kidney injury OR AB=kidney injury) OR (TI=hospital duration OR AB=hospital duration) OR (TI=postoperative complications OR AB=postoperative complications) OR (TI=cerebral edema OR AB=cerebral edema) OR (TI=vasospasm OR AB=vasospasm) OR (TI=Modified Rankin scale OR AB=Modified Rankin scale) OR (TI=total fluid OR AB=total fluid) | 1,242,843 |
| | #4 | #1 AND #2 AND #3 AND (English[Filter]) | 14 |

## Supplemental digital content 4

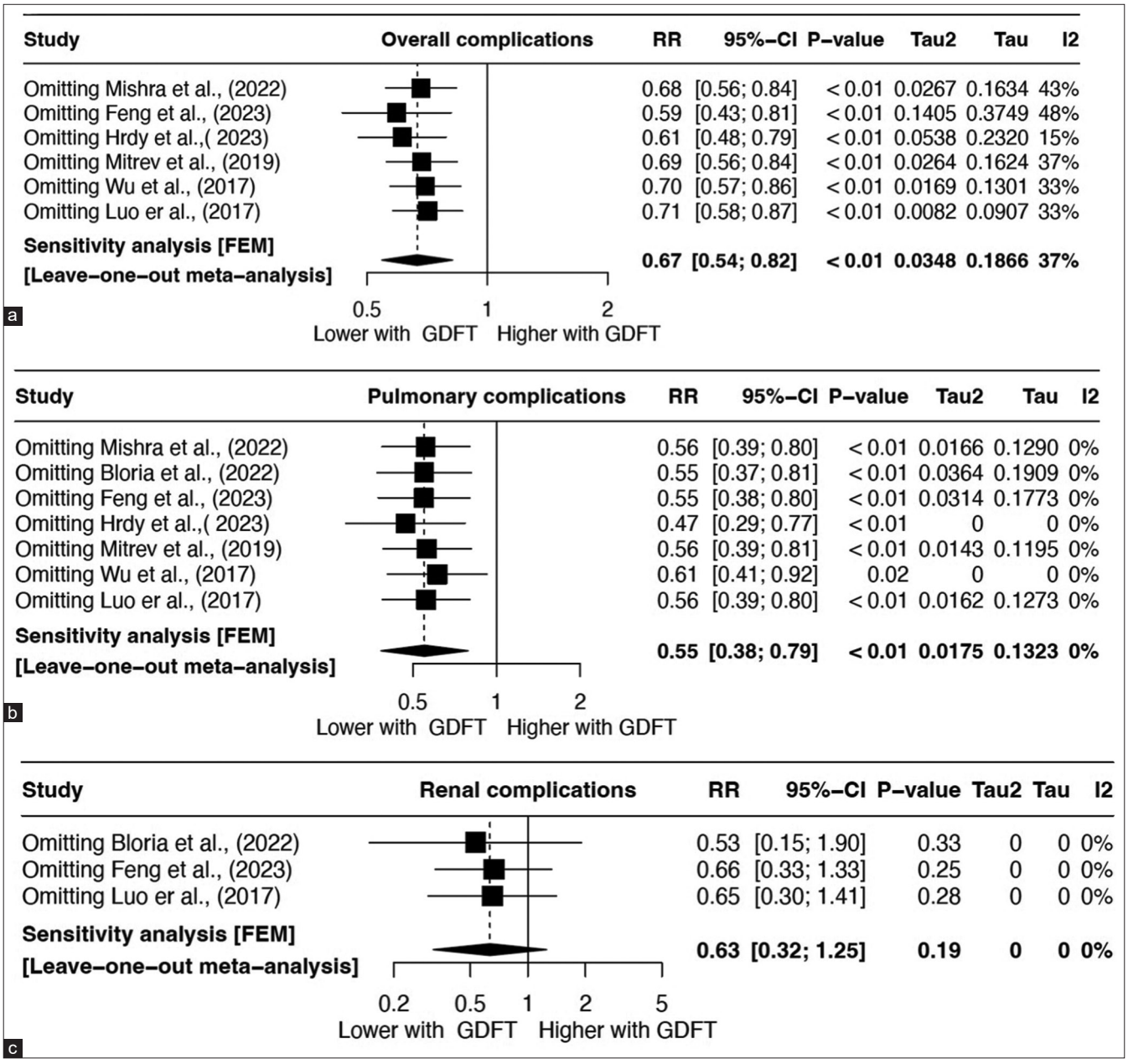


**Figure 1S:** Leave-one-out analysis of the proportion data: (a) overall complications; (b) pulmonary complications; (c) renal complications. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, RR = risk ratio

## Supplemental digital content 5

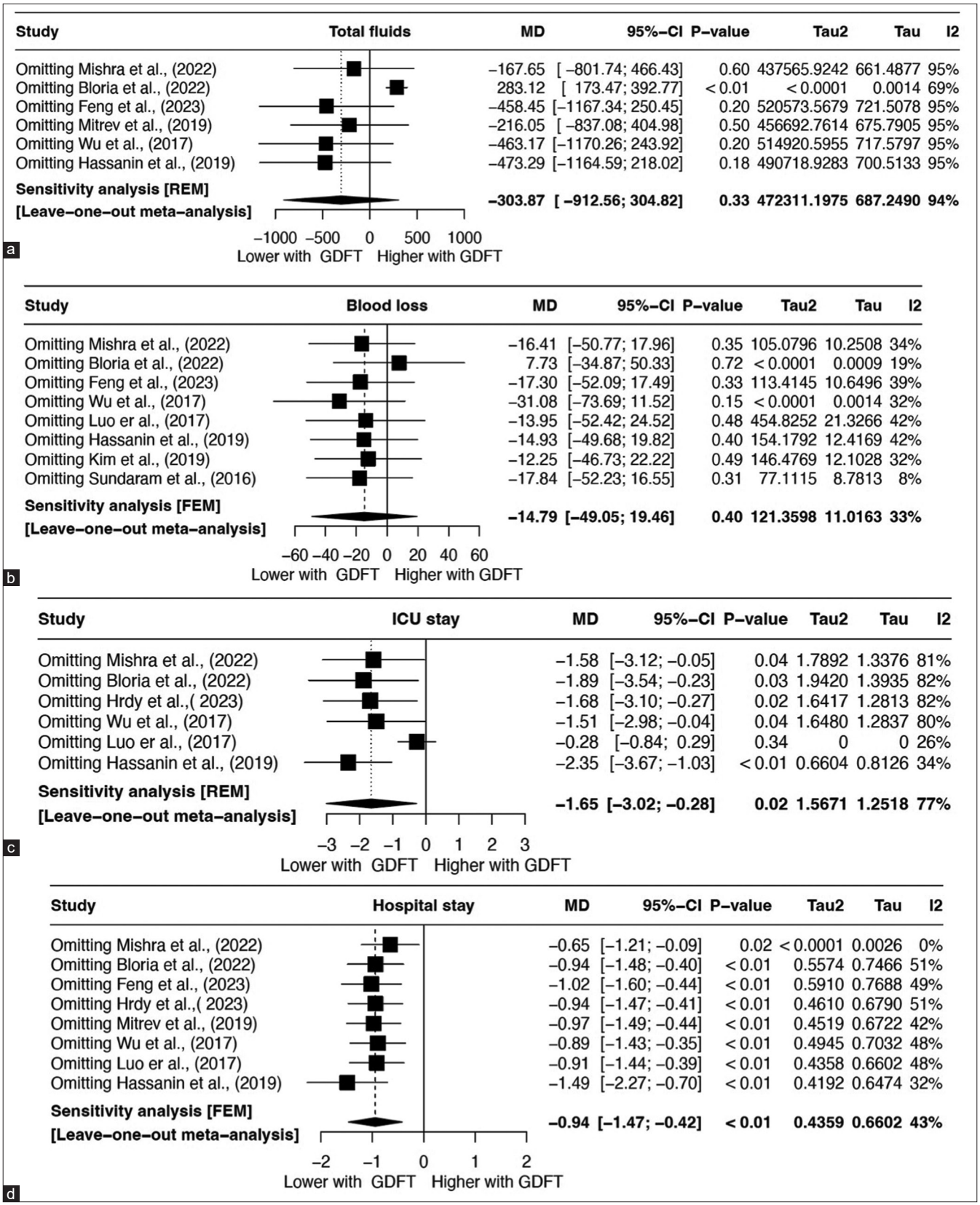


**Figure 2S:** Leave-one-out analysis of the mean difference: (a) total fluids; (b) blood loss; (c) ICU stay; (d) hospital stay. CI = confidence interval, FEM = fixed effects model, GDFT = goal-directed fluid therapy, ICU = intensive care unit, MD = mean difference, REM = random effects model

| Table S3: Trial sequential analysis |
|---|
| This is a retrospective meta-analysis sample size calculation. The sample size calculation assumes a two-sided test, equal group sizes, a type-I error of 0.01428571 and a type-II error of 0.2 |
| The type-1 error is based on *P* value adjustment for the seven critical outcomes used for assessing evidence quality.[1] TSA could not be computed for neurological outcomes and overall complications |
| **Blood loss** |
| Minimal clinically important mean difference: 100 ml |
| Fixed effects required information size: |
| The number of participants required for a fixed-effect meta-analysis has reached a certain point |
| Random effects required information size: |
| Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached |
| Adjusted by inconsistency (I^2): The number of required participants for a random effects meta-analysis is reached |
| **Hospital stay** |
| Minimal clinically important mean difference: 3 days |
| Fixed effects required information size: |
| The number of participants required for a fixed-effect meta-analysis has reached a certain point |
| Random effects required information size: |
| Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached |
| Adjusted by inconsistency (I^2): The number of required participants for a random effects meta-analysis is reached |
| **ICU stay** |
| Minimal clinically important mean difference: 2 days |
| Fixed effects required information size: |
| The number of participants required for a fixed-effect meta-analysis has reached a certain point |
| Random effects required information size: |
| Adjusted by inconsistency (D^2): The number of required participants for a random effects meta-analysis is reached |
| Adjusted by inconsistency (I^2): The number of required participants for a random effects meta-analysis is reached |
| **Pulmonary complications** |
| Minimal clinically important risk reduction: 5% |
| Fixed effects required information size: 51,957 participants in total are additionally required |
| **Renal complications** |
| Minimal clinically important risk reduction: 5% |
| Fixed effects required information size: 130,078 participants in total are additionally required |
| **Neurological outcomes and overall complications** |
| Could not be computed |
| 1. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14. |

TSA=Trial sequential analysis