

# Restrictive versus liberal fluid therapy in geriatric patients undergoing major abdominal surgery: a randomized controlled trial

**Bin Cai**

Guangdong provincial people's hospital <https://orcid.org/0000-0001-9237-2220>

**JiaTong Chen**

Guangdong provincial people's hospital

**Yin Kang**

Guangdong provincial people's hospital

**Dongnan Yu**

Guangdong provincial people's hospital

**Jinfeng Wei**

Guangdong provincial people's hospital

**JieYuan Chen**

Guangdong provincial people's hospital

**Sheng Wang** (✉ [shengwang\\_gz@163.com](mailto:shengwang_gz@163.com))

<https://orcid.org/0000-0003-0065-0102>

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## Research article

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# Abstract

**BACKGROUND:** The optimal fluid therapy in elderly patients undergoing major abdominal surgery remains unclear. Although some trials have reported a restrictive fluid therapy may lead to better outcomes, there is no evidence whether it is suitable for elderly patients. **METHODS:** In a double-blinded pragmatic trial, 107 elderly patients undergoing major abdominal surgery were randomized to receive either a liberal (L group) or restrictive intravenous-fluid therapy (R group). The postoperative fluid therapy was similar in the two groups. The primary outcome was vital organ injury included Myocardial injury after noncardiac surgery (MINS) and acute kidney injury (AKI), the secondary outcomes included hypotension needed intervention intraoperatively, length of stay (LOS), death and other complications defined up to 30 days. Analysis was performed by intention-to-treat. **RESULT:** 50 patients in the L group had an average intravenous fluid of 1943ml, as compared to 1295.61ml in 57 patients in the R group ( $P < 0.001$ ). The baseline Characteristics and operative details were similar between the groups. Patients in the L group had a lower rate of AKI (10% vs 35.1%,  $P = 0.002$ ) and surgical-site infection (0 vs 10.5%,  $P = 0.029$ ) than in the R group (MINS (20% vs 20.8%,  $P = 0.724$ ) and the other postoperative complications showed no differences between two groups. One patient died in the R group. No significant difference was found for the length of hospital stay [median(range) L: 15(8-49) vs R: 17(8-80);  $P = 0.27$ ]. The follow-up was 30 days. **CONCLUSION:** In geriatric patients undergoing major abdominal surgery, a liberal fluid regimen was associated with a lower rate of AKI and postoperative infection than restrictive fluid regimen and did not increase the risk of postoperative complications. Trial registration: ChiCTR1800019022. Registered 21 October 2018

## Background

Major abdominal surgery is associated with many risks, especially in elderly patients with their multisystem physiologic decline and increased vulnerability to stressors. Despite the development of surgical skill and perioperative care, complications after major abdominal surgery remain a significant cause of increased morbidity, mortality, and health care costs in China. Recently attention has turned to the intraoperative fluid management, which might have influence on outcomes.

Some trials reported that a restrictive fluid therapy led to fewer complications and shorten LOS[1, 2]. Recent perioperative guidelines and consensus statements also supported restrictive fluid therapy[3, 4]. Nevertheless, the evidences for restriction of perioperative fluid therapy is inconclusive[5-7] and these findings were not always replicated. A restrictive intravenous-fluid regimen might increase rate of acute kidney injury (AKI)[5] and it is more likely to treat hypotension with vasopressor therapy, impairing the perfusion of organ.

Historically perioperative fluid management tended to more liberal. Since the 1950s, when the so called 'third space losses' was claimed that fluids are redistributed to a third space, perioperative fluid management should replace of such losses with a large amount of crystalloid. Besides, clinicians

administer liberal volumes of fluids perioperative for concerning about the preoperative dehydration and unstable of hemodynamics intraoperatively.

Such liberal fluid infusion is also controversial by increasing the risk of cardiopulmonary complications, enteral edema, nausea and vomiting and prolonging LOS[8]. Elderly patients are vulnerable to excessive fluid management because of their decline of multisystem physiologic function. Too much intravenous-fluid might cause disfunction of vital organs and led to more postoperative complications.

Since the most effective fluid regimen is unclear and the ubiquity of fluid therapy in major abdominal surgery, we conducted this trial to test the liberal (more traditional) against restrictive fluid therapy in elderly patients.

## Methods

We enrolled 107 patients who had planned for major abdominal surgery in Guangdong provincial people's hospital between November 2018 and April 2019. Patients were eligible if they planned for major abdominal surgery and at least 65 years old, an expected operative duration of at least 2 hours and 3 days of hospital stay. Urgent or time-critical surgery, liver resection, or less extensive surgery (laparoscopic cholecystectomy or closure of colostomy) , or patients with end-stage kidney failure requiring dialysis were excluded. Patients allergic to artificial colloid fluid or experienced intraoperative hemorrhagic shock were also excluded. Written informed consent was obtained from all participants before the day of surgery (Fig 1) . The trial has been approved by the Research Ethics committee of Guangdong Provincial People's Hospital (NO. GDREC2018575H) and registered in Chinese Clinical Trial Registry (ChiCTR1800019022) .

Patients were randomized to either restrictive fluid therapy group (R group) or liberal fluid therapy group (L group) in the preparing room by one assigned anesthetist, so the patients and surgeons were kept blinded. The randomization sequence was made by another research member and delivered in sealed consecutively numbered envelopes. The blinding of all research staff members were kept until the end of the trial, but the attending anesthetist had knowledge of the group assignments in order to perform different intravenous-fluid therapy during operation.

### Trial treatments

Perioperative surgery care was conducted in line with enhanced recovery principles. Mechanical bowel preparation was discouraged; all patients received prophylactic antibiotics and were allowed to drink clear liquid before 2 hours of surgery[4].

Patients were premedicated with penehyclidine (0.5mg) . General anesthesia was induced with midazolam (0.05mg/kg) , propofol (1-2mg/kg) , sulfentanyl (0.3ug/kg) and cisatracurium (0.2mg/kg) . The anesthesia was maintained with sevoflurane or propofol and remifentanyl. Narcotrend Index was also used to optimize the depth of anesthesia (D2-E0) . If the patient underwent open surgery, transversus abdominis plane block was performed with ropivacaine. Patients were monitored with electrocardiogram

(ECG) , heart rate(HR) , non-invasive blood pressure, SpO<sub>2</sub>, end tidal CO<sub>2</sub> and body temperature. Central venous pressure and arterial pressure monitoring was left to the discretion of the anesthetist and hypothermia was avoided by employing routine intraoperative warming strategies.

The liberal fluid therapy was defined as more traditional infusion therapy[5, 9] for major abdominal surgery with a bolus of balanced salt crystalloid solution at a dose of 10 ml/kg when induction, followed by a dose of 8-10 ml/kg per hour until the end of surgery. The latter infusion regimen could be further reduced after 4 hours if clinical indicated. If the patient was found hypotension, an extra bolus of 250 ml crystalloid solution would be considered first without evidence of fluid overload.

The restrictive fluid therapy was defined to provide a zero fluid balance[5, 10]. A rate of 5ml/kg was administered during induction. An infusion of balanced salt crystalloid solution at a dose of 4-5 ml/kg per hour was maintained until the end of surgery. Vasopressors (deoxyepinephrine or norepinephrine) could be first considered for treating hypotension when excluded the possibility of hypovolemia. The total administration of fluid during surgery was expected to be approximately half that in the liberal fluid group. For patients with a body weight of more than 100kg, the fluid volumes were calculated based on 100 kg.

Intraoperative oliguria should be intervened by administration of extra 100 to 200ml crystalloid fluid in both groups if least than 0.3 ml/kg/h, because it might be a warning of hypovolemia and increase the risk of AKI postoperative[11].

Both groups could use colloid fluid (hydroxyethyl starch 130/0.4 or modified fluid gelatin) to replace blood loss (1:1) or packed red blood cell which depended on hematocrit and complication of the patients. If blood loss was large, plasma or thrombocytes were added (Fig 2) . The amount of fluid at the first 24h postoperatively were similar between two groups (2ml/kg per hour) .

### **Postoperative care**

Standardized postoperative care was provided on surgery ward in both groups, administration to the Intensive Care Unit was at the discretion of the surgeon and anesthetist. Oral intake and early mobilization was encouraged when the patient was tolerated. Pain after surgery was treated with flurbiprofen, non-steroidal anti-inflammatory drug, or dezocine as needed.

If more fluid were required, balanced saline solution was administered on physician preference and modified fluid gelatin was permitted to restore volume if hypovolemia was occurred.

Primary outcomes was vital organ injury included Myocardial injury after noncardiac surgery (MINS) and acute kidney injury (AKI), the secondary outcomes included hypotension needed intervention intraoperatively, length of stay (LOS) , death and other complications defined up to 30 days. Diagnosis criteria was according to kidney disease: improving global outcomes (KDIGO)[12] or needed to renal replacement therapy (RRT). Secondary outcomes were hypotension needed intervention, other complications up to 30 days and LOS. Patients had blood collected for High Sensitivity Troponin T (Hs-TnT) assay preoperatively and on days 1, 2 after surgery for detecting MINS[13]. A complication was

recorded if clinical treatment was necessary (table 2) . Major complications defined as the life-threatening complications, including reoperation, unplanned transfer to intensive care unit and anastomotic leakage. Postoperative outcomes were recorded by an investigator blinded to the group allocation. The investigator had no involvement in perioperative decision-making or postoperative care.

## Statistical analysis

The number of patients included in this trial was calculated based on our previous data and other published researches. Considering a power of 0.85 and a significance level of 0.05 will require 48 patients per group. As a result, we planned to enroll 110 patients (55 per group) . No interim analysis was performed.

Independent T Test were used to estimate if the data was continuous and normally distributed. Mann-Whitney U tests or chi-square analysis were indicated if discontinuous or not normal distribution was found through a Kolmogorov-smirnov test. A Fisher exact test was performed when the number was less than expected. Significance was set at the 0.05 level and all P-values reported were two-tailed. Data were analyzed using SPSS 19.0 software.

## Results

110 patients fulfilled the criteria and 107 were enrolled in two groups: 57 in the L group and 50 in the R group. 3 patients were excluded (1 for administration of non-protocol fluid and 2 withdrew their consent) . All patients were included in the intention to treat analysis. No differences between the groups were found for basis data, diagnosis or surgical data (table 1) .

The total intraoperative volume of fluid was 1943ml (443.894) in L group and 1295.61ml (465.054) in R group ( $P<0.001$ ) . There were no significant difference in intraoperative hypotension needed intervention (52%vs57.9%,  $P=0.541$ ) between groups, neither was the postoperative ICU stay rate (12% vs 12.3%,  $P=1$ ) . No significant difference were found in any product of blood component and lactate levels measured at the end of surgery (0.68mmol/L vs 0.77mmol/L,  $P=0.183$ ) .

20 (35.1%) patients developed AKI in the R group and 5 (10%) in the L group ( $P=0.002$ ) assessed by the KDIGO classification. MINS (20% vs 20.8%,  $P=0.81$ ) didn't have obvious difference between groups. But wound infection after surgery in L group was significantly lower than in the R group (0 vs 10.5%,  $P=0.029$ ) . No other difference was found in postoperative complications (table 2) .

No significant difference were found in LOS (15 days vs 17 days,  $P=0.27$ ) , ICU stay time or flatus passed time after surgery (39.89 hours vs 45.5 hours,  $P=0.192$ ) and the readmission rate (2% vs 3.5%,) up to 30days between the groups. One patient died in the R group.

## Discussion

Perioperative fluid management impacts outcomes and plays a pivotal role in perioperative management. Defining and attaining an adequate volume is complex and the fluid deficit before surgery varies among

individuals. Goal-directed therapy (GDT) based on the optimization of flow-related variables may be the best approach for fluid administration, but some studies [14, 15] showed a totally different conclusion and did not encourage to apply GDT in every patient.

Traditional fluid therapy can deliver up to 7 liters on the day of surgery in order to make up for the loss of preoperative fasting, anesthesia-induced vasodilation and accumulation of fluid in extravascular spaces[16, 17]. Previous some trials[18-20] showed that such liberal fluid therapy could lead to tissue edema and increased interstitial lung water, leading to further complications.

ERAS (enhanced recovery after surgery) pathway is a clinical care guideline proposed in last 90th[21, 22], aiming at attenuating surgery stress, promoting early recovery among patients undergoing major abdominal surgery and decreasing the Length Of Stay (LOS) . Avoiding too much fluid or a more restrictive fluid regimen is recommended in recent ERAS guidelines[23, 24]. But these evidence seem not inconclusive in major abdominal surgery[18, 25, 26]. Especially, too restriction of fluid regimen may increase the rate of AKI and hypotension perioperatively[27]. AKI in the perioperative period is a common complication in geriatric patients associated with increased morbidity and mortality. Recent update on perioperative AKI review[28] emphasized adequate perioperative fluid to ensure hemodynamic stability and the perfusion of kidney. Oliguria could be the response for either hypovolemia or normal activity of antidiuretic hormone. In our trial, no difference was found (2% vs 3.5%,  $P=1$ ) in oliguria during surgery between groups. Some studies reported that it shouldn't be use as an indication for renal injury[29], nor is there any evidence that shows diuretics protect against AKI[30]. But it is associated with adverse outcomes[28] and too restriction of fluid therapy might increase the need for vasopressor and worsen the perfusion of organs. The diagnosis of AKI postoperatively in our trial, therefore, had combined both urine output and serum creatine. Providing sufficient perfusion of kidney will be the key point in avoiding AKI perioperatively and that might be explained why liberal group did have a low risk of AKI in our trial(5% vs 20%,  $P=0.002$ ), which was similar to the previous trial[5]. We also identified a higher rate of surgical-site infection in the R group, possibly caused by the hypoperfusion of anastomotic or the wound.

Myocardial injury after noncardiac surgery (MINS) is defined as myocardial injury that occurs during or within 30 days after surgery, an independently risk factor for long-term outcome[13], and it is more common in elderly patients perioperatively. Recent perioperative guidelines[31, 32] have recommended patients >65 years measure troponin. It is rather common in elderly patients. Previous studies have found that an elevated Hs-TnT is associated with long-term mortality even without ischemic symptom[13]. In our trial, MINS was diagnosed by an elevated Hs-TnT change of 5 ng/L or higher. Our first hypothesis was that liberal fluid therapy could increase the injury of cardia in elderly patients and MINS in the L group might be more obvious than R group. However, no significant difference was found (20% vs 20.8%,  $P=0.724$ ) in our trial, nor difference were found in other complications up to 30days. But it should not to be the evidence to support the traditional fluid regimen, it should be explained that relatively liberal fluid therapy is safer than restriction ones and may have more strength in elderly patients, not increase the risk of MINS and other complications.

## Limitations of the study

Our trial has several limitations. First, our anesthetist took part in this trial could not be blinded to the procedure, and this might introduce bias in documentation and some outcome monitoring. Second, we didn't separate the laparoscopic surgery from open surgery. One study[33] showed no difference outcome in different fluid strategies and there were no evidences existed that patients undergoing laparoscopic surgery should be treated differently from open surgery. Third, we did not analysis the amount of fluid included 24hours postoperatively when most intravenous fluid is given and that might cause some bias in outcomes and many patients could not be weighed on days 1 to 3. Finally, these results are limited to shorty-term outcomes, however, some authors have demonstrated the impact of early postoperative complications on long-term outcomes[28, 34].

## Conclusions:

In Conclusion, in elderly patients undergoing major abdominal surgery, a liberal fluid therapy was associated with a lower rate of AKI than restrictive fluid therapy and did not increase the risk of postoperative complications.

## List Of Abbreviations

abbreviations	means
L group	Liberal fluid therapy group
R group	Restrictive fluid therapy group
MINS	Myocardial injury after noncardiac surgery
AKI	Acute kidney injury
LOS	Length of stay
SpO2	Pulse Oxygen Saturation
ECG	electrocardiogram
HR	Heart rate
RRT	Renal replacement therapy
Hs-TnT	High sensitivity troponin T
ICU	Intensive care unit
GDT	Goal directed therapy
ERAS	Enhanced recovery after surgery

## Declarations

Ethics approval and consent to participate: This prospective randomized study was approved by the Research Ethics committee of Guangdong Provincial People's Hospital (NO. GDREC2018575H) and written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and material: The full study protocol and raw data set can be obtained from Bin Cai (caibingz@qq.com)

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Authors' Information: 1: Department of Anesthesiology, Guangdong Provincial people's hospital, Guangdong Cardiovascular Institute, Guangdong Academy of Medical Sciences, Guangzhou, China. 510080. 2: Shantou University Medical College, Shantou, Guangdong Province, China. 515000.

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## Tables

**Table 1 Baseline Characteristics and operative details**

	Liberal group(N=50)	Restrictive group(N=57)	p-value
Age (yr)	72.5(7.1)	73.3(6.8)	0.582
Male sex (%)	26(52%)	34(60.7%)	0.243
Weight (kg)	57.6(9.5)	59.7(10.0)	0.271
ASA †			0.662
I	3(6%)	5(8.8%)	0.861
II	31(62%)	30(52.6%)	0.329
III	16(32%)	22(38.6%)	0.477
Type of surgery			
gastric	12(24%)	15(26.3%)	0.783
colonic	27(54%)	29(50.9%)	0.747
rectal	11(22%)	13(22.8%)	0.920
Co-existing disease			
None	5	3	0.469
Hypertension	26	32	0.668
Ischaemic heart disease	36	34	0.180
Myocardial disease	1	4	0.369
Atrial fibrillation	5	7	0.709
Diabetes mellitus	9	10	0.951
Other heart disease	12	10	0.410
Stoke	2	1	0.598
Other CNS disease	0	1	1.0
Intraoperative Characteristic			
Duration of surgery(mins)☒	241.3(111.04)	238.421(68.48☒)	0.870
Planned postoperative care in ICU-no.(%)	6(12.0%)	7☒12.3%☒	1.0
Median Blood loss (median, IQR)(ml)	80(50-100)	60(50-100)	0.531
Fluids(ml)			
Crystalloid	1500(455.69)	978.9(653.35)	<b>&lt;0.001</b>
Colloid	387(273.1)	355(210.6)	0.500
Packed RBC, (median, IQR) (unit)	0(0-4)	0 (0-4)	1.0
Other blood product(median, IQR)(ml) *	0(0-400)	0(0-400)	1.0
Total intravenous fluid(ml)	1943(443.894)	1295.61(465.054)	<b>&lt;0.001</b>
Open surgery, no.(%)	7(14%)	7(12.3%)	0.792
Oliguria during operation, no.(%) ☒	1(2%)	2(3.5%)	1.0
Urine output(ml)	362.6(34.557)	282.11(22.640)	<b>0.049</b>

Population data are listed as value(%) or mean(standard difference). \*other blood product are flesh frozen plasma. † ASA status are using Kruskal-Wallis H test for total and each group difference. ☒Definition of oliguria are least than 0.3 ml/kg/h during operation.

**Table 2 Postoperative outcomes**

variables	Liberal group(N=50)	Restrictive group(N=57)	p-value
AKI (NO.,%) †	5(10%)	20(35.1%)	<b>0.002</b>
MINS(NO.,%) ※	10(20%)	13(20.8%)	0.724
Lactate level after surgery(mean, SE) (mmol/L)	0.68(0.05)	0.77(0.05)	0.183
Hypotension needed intervened	26(52%)	33(57.9%)	0.541
Flatus passed(mean, SE) (hours)	39.89(3.2)	45.50(2.78)	0.192
Major complication			
Mortality	0	0	1.0
Unplanned transform to intensive care unit	0	2(3.5%)	0.497
Bleeding requiring a redo surgery	0	0	1.0
Anastomotic leakage	2(4%)	2(3.5%)	1.0
Wound infection	0	6(10.5%)	<b>0.029</b>
VAS score at day 3 postoperative(mean, SE)	2.38(0.16)	2.46(0.14)	0.692
LOS			
ICU(hours)(median, IQR)	0(0-432)	0(0-1008)	0.955
Hospital(days)(median, IQR)	15(8-49)	17(8-80)	0.270
Death	0	1	1.0
30 days readmission *	1(2%)	2(3.5%)	1.0

Outcome data are presented as value(%) or mean and difference. Indicates significant results with P values<0.05. ※ MINS diagnosis was followed as a elevation of Hs-TnT more than 5ng/l, or an absolute Hs-TnT was large than 14ng/ml. † AKI(acute kidney injury) defined as KDIGO guideline: either an increase of serum creatinine or a reduced urine output: In an increase of serum creatinine  $\geq 0.3$  mg/dL (26.5  $\mu$ mol/L) within 48 h or an increase of serum creatinine by  $\geq 1.5$ -fold above baseline, known or assumed to have occurred within 7 days, or urine volume <0.5 mL/kg/h for 6 h. \* data was collected among 99 patients

## Figures

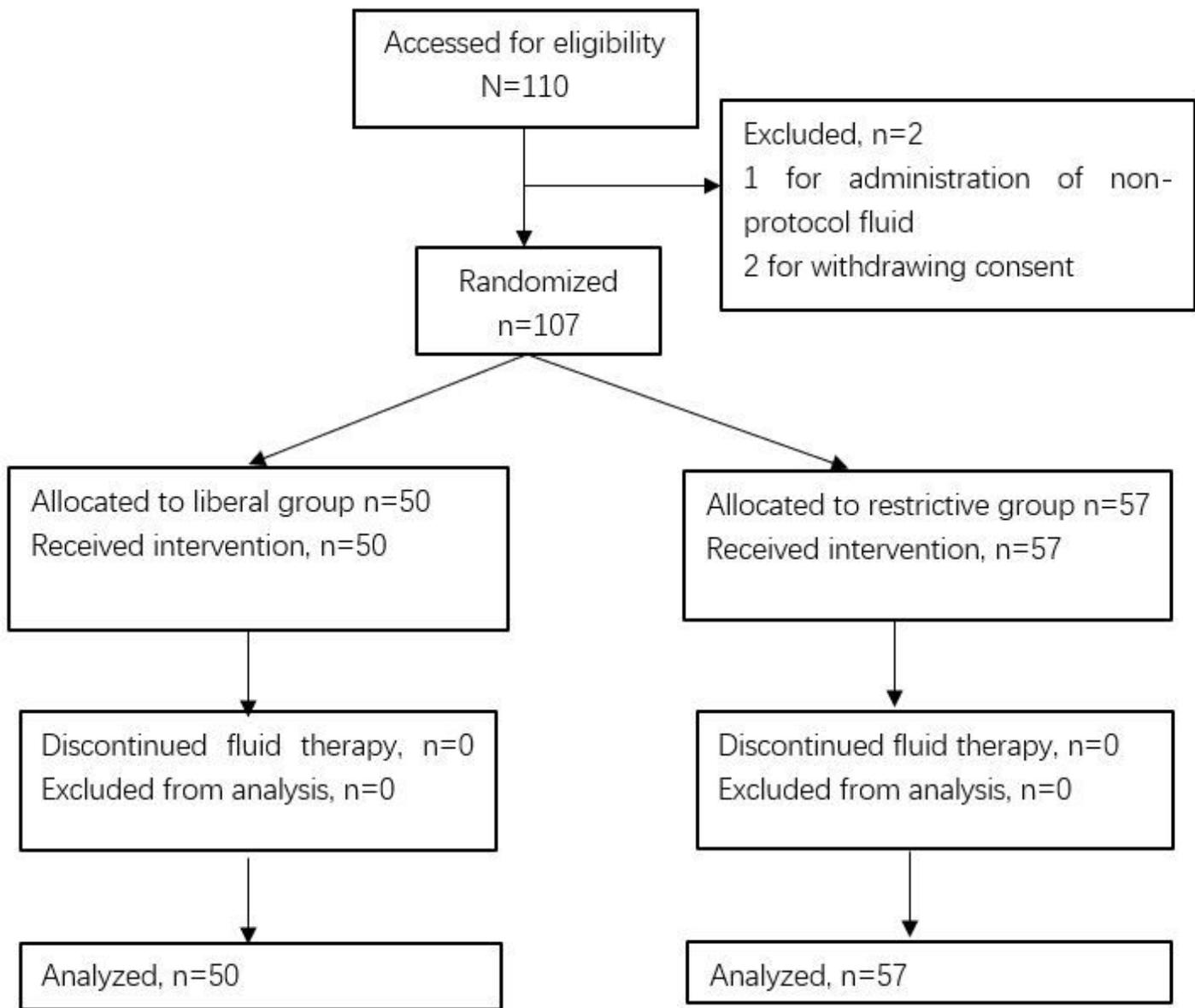


Figure 1

CONSORT diagram

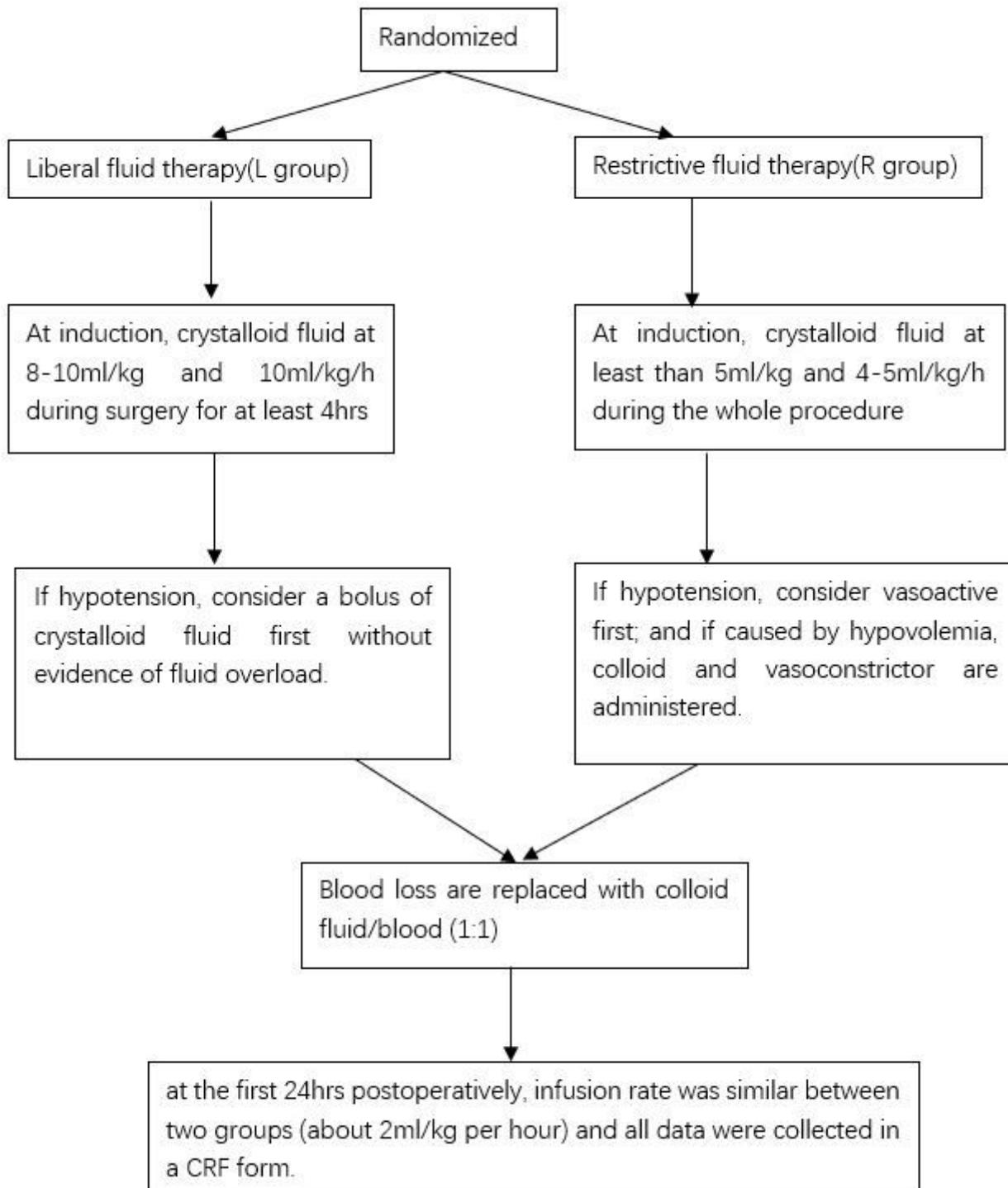


Figure 2

Intraoperative Fluid Administration Algorithm

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [CONSORTFlowDiagram.doc](#)