Queen's UNIVERSITY

DEPARTMENT OF ANESTHESIOLOGY

JOURNAL CLUB

Monday, 03 October, 2022
1800 HOURS

LOCATION:
River Mill Restaurant
2 Cataraqui Street

PRESENTING ARTICLES:
Dr. Yannis Amador Godoy &
Dr. Theunis Van Zyl

This program is possible by an educational grant from Medtronic

SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS
ANESTHESIOLOGY JOURNAL CLUB
QUEEN'S UNIVERSITY

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants.

GENERAL

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

INTRODUCTION

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

METHODOLOGY

1. Study design:
    a) Clinical trial vs. systematic review/meta-analysis
    b) Prospective vs. retrospective
    c) Observational vs. Experimental
    d) Randomized or not
    e) Blinded or not

2. Population studied:
    a) Human, animal, other
    b) Justification
    c) Control groups: experimental vs. historical
    d) Is the sample size/power calculated, and how?
    e) Is the population similar to your own practice?
    f) Single vs. multi-centre

3. Is the study ethically sound?
    a) Clinical equipoise
    b) Does treatment meet standard of care (esp controls)?
    c) Appropriate consent and institutional ethics approval

4. Exclusions: what groups are excluded and why?

5. Experimental protocol
    a) Is it designed to test the hypothesis?

b) Is it detailed enough to be reproducible?
c) Is the methodology validated?
d) Are the drugs/equipment used detailed?
e) How does the randomization take place?

6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

RESULTS

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

DISCUSSION

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

APPLICABILITY OF THE PAPER

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery

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Chinese Translation 中文翻译

Article | Figures/Media

Metrics

35 References
399 Citing Articles
Letters
Related Articles

Abstract

BACKGROUND

Guidelines to promote the early recovery of patients undergoing major surgery recommend a restrictive intravenous-fluid strategy for abdominal surgery. However, the supporting evidence is limited, and there is concern about impaired organ perfusion.

METHODS

In a pragmatic, international trial, we randomly assigned 3000 patients who had an increased risk of complications while undergoing major abdominal surgery to receive a restrictive or liberal intravenous-fluid regimen during and up to 24 hours after surgery. The primary outcome was disability-free survival at 1 year. Key secondary outcomes were acute kidney injury at 30 days, renal-replacement therapy at 90 days, and a composite of septic complications, surgical-site infection, or death.

RESULTS

During and up to 24 hours after surgery, 1490 patients in the restrictive fluid group had a median intravenous-fluid intake of 3.7 liters (interquartile range, 2.9 to 4.9), as compared with 6.1 liters (interquartile range, 5.0 to 7.4) in 1493 patients in the liberal fluid group (P<0.001). The rate of disability-free survival at 1 year was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (hazard ratio for death or disability, 1.05; 95% confidence interval, 0.88 to 1.24; P=0.61). The rate of acute kidney injury was 8.6% in the restrictive fluid group and 5.0% in the liberal fluid group (P<0.001). The rate of septic complications or death was 21.8% in the restrictive fluid group and 19.8% in the liberal fluid group (P=0.19); rates of surgical-site infection (16.5% vs. 13.6%, P=0.02) and renal-replacement therapy (0.9% vs. 0.3%, P=0.048) were higher in the restrictive fluid group, but the between-group difference was not significant after adjustment for multiple testing.

CONCLUSIONS

Among patients at increased risk for complications during major abdominal surgery, a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen and was associated with a higher rate of acute kidney injury. (Funded by the Australian National Health and Medical Research Council and others; RELIEF ClinicalTrials.gov number, NCT01424150.)

Introduction

Each year, at least 310 million patients undergo major surgery worldwide,[1] procedures that involve the administration of intravenous fluids. Clinicians have traditionally administered generous amounts of intravenous fluids perioperatively to correct for preoperative fasting and other fluid deficits, anesthesia-induced vasodilation, hemorrhage, and accumulation of fluid in extravascular spaces[2] and to enhance tissue oxygen delivery and maintain urine output.[3-5] Occult hypovolemia may occur in up to 60% of such patients.[4,6,7]

Traditional intravenous-fluid regimens that are administered during abdominal surgery deliver up to 7 liters of fluid on the day of surgery.[8-10] Such regimens can lead to tissue edema and weight gain of 3 to 6 kg.[8,11,12] Some small trials have shown that a more restrictive fluid regimen led to fewer complications and a shorter hospital stay,[9,11,13] and recent consensus statements support fluid restriction.[12,14,15] Restricting fluids to achieve zero balance is also a key component of enhanced recovery after surgery (ERAS) pathways, a perioperative care guideline that is designed to promote early recovery among patients undergoing major surgery.[12,14,16] However, the evidence for fluid restriction during and immediately after abdominal surgery

is inconclusive.[12,15-17] Fluid restriction could increase the risk of hypotension and decrease perfusion in the kidney and other vital organs, leading to organ dysfunction, but excessive intravenous-fluid infusion may increase the risk of pulmonary complications,[18] acute kidney injury,[19] sepsis,[20] and poor wound healing.[21]

Since the most effective intravenous-fluid regimen is unclear,[12,22] we conducted the Restrictive versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) trial to compare a restrictive fluid regimen with a more traditional (liberal) regimen in patients who had an increased risk of complications while undergoing major abdominal surgery. Our primary hypothesis was that a restrictive fluid regimen in adults undergoing such surgery would lead to a lower rate of complications and a higher rate of disability-free survival than a liberal fluid regimen.[22]

Methods

TRIAL DESIGN

The RELIEF trial was an international, randomized, assessor-blinded trial comparing a restrictive intravenous-fluid regimen with a liberal regimen that represented traditional care in patients undergoing major abdominal surgery. The rationale and design of our trial have been reported previously.[22] The trial was funded by the Australian National Health and Medical Research Council, the Health Research Council of New Zealand, the Australian and New Zealand College of Anaesthetists, and Monash University. The trial protocol (available with the full text of this article at NEJM.org) was approved by the institutional review board at each site.

The members of the steering committee (who are listed in the Supplementary Appendix, available at NEJM.org) designed the trial, gathered and analyzed the data, prepared the manuscript, and together with their coauthors made the decision to submit the manuscript for publication. The members of the steering committee vouch for the accuracy and completeness of the data set and adherence to the trial protocol and statistical analysis plan. There was no commercial involvement in the trial.

PATIENT SELECTION AND RANDOMIZATION

We studied adults who had an increased risk of complications while undergoing major abdominal surgery that included a skin incision, an expected operative duration of at least 2 hours, and an expected hospital stay of at least 3 days. Surgical-risk criteria included an age of at least 70 years or the presence of heart disease, diabetes, renal impairment, or morbid obesity. (Details regarding the categories of increased risk are provided in the Supplementary Appendix.) Patients were excluded if they were undergoing urgent or time-critical surgery, liver resection, or less extensive surgery (e.g., laparoscopic cholecystectomy) or if they had end-stage kidney failure requiring dialysis. All the patients provided written informed consent.

After enrollment, on the day of surgery, patients were asked to complete the 12-item World Health Organization Disability Assessment Schedule (WHODAS).[23] They were then randomly assigned in a 1:1

ratio to a trial group in permuted blocks and stratified according to site and planned postoperative destination (critical care or hospital ward) by means of a Web-based service.

TRIAL TREATMENTS

The liberal intravenous-fluid regimen was designed to reflect traditional practices for abdominal surgery.[8-10,24,25] A bolus of a balanced salt crystalloid solution was administered at a dose of 10 ml per kilogram of body weight during the induction of anesthesia, followed by a dose of 8 ml per kilogram per hour until the end of surgery. The perioperative dose could be further reduced after 4 hours if clinically indicated. For patients with a body weight of more than 100 kg, fluid volumes were calculated on the basis of a maximal body weight of 100 kg. Fluid infusion was continued postoperatively at a dose of 1.5 ml per kilogram per hour for at least 24 hours, but this dose could be reduced if there was evidence of fluid overload and no hypotension, or increased if there was evidence of hypovolemia or hypotension.

The restrictive intravenous-fluid regimen was designed to provide a net zero fluid balance.[9,11,14] Induction of anesthesia was accompanied by an intravenous-fluid bolus of no more than 5 ml per kilogram; no other intravenous fluids were to be administered before surgery unless indicated if using a goal-directed device (esophageal Doppler or pulse wave analyzer). An infusion of a balanced salt crystalloid solution at a dose of 5 ml per kilogram per hour was administered until the end of surgery. Intravenous fluids were continued postoperatively at a dose of 0.8 ml per kilogram per hour. The rate of postoperative fluid replacement could be adjusted as outlined for the liberal fluid group, except that the use of vasopressors could first be considered for treating hypotension without evidence of hypovolemia. The total administration of fluid during the first 24-hour period was expected to be approximately half that in the liberal fluid group.

Bolus colloid or blood could be used intraoperatively in the two groups to replace blood loss (milliliter for milliliter). Alternative fluid types (other crystalloid, dextrose, or colloid) and electrolytes were allowed postoperatively to account for local preferences and blood biochemical findings. Oliguria was not used as an indication for the additional administration of intravenous fluid. All other perioperative care was performed according to the discretion and practices of local clinicians (see the **Supplementary Appendix**).

BLINDING AND DATA QUALITY

The attending anesthesiologist and most medical and nursing staff members who were caring for patients on the ward had knowledge of the group assignments. All research staff members who were responsible for the primary outcome assessment were not aware of group assignments.

Members of a clinical end-points committee who did not participate in the trial adjudicated all secondary outcome events in a blinded manner. The committee members conducted trial-center visits with random audits during the trial, and a data-quality committee monitored data completion and accuracy. An independent data safety and monitoring committee monitored the trial for safety, which included a review of the results of a formal interim analysis that was performed after 1632 patients had undergone randomization.

MEASUREMENTS AND PATIENT FOLLOW-UP

Patients were followed during their hospital admission and up to 1 year after surgery.[22] We measured the quality of the recovery of each patient using a validated 15-item quality-of-recovery scale (QoR-15).[26] On day 30, the medical records of all the patients were reviewed, and the patients were contacted to ascertain whether any of the primary or secondary outcomes had occurred. Research staff members collated source documentation for any outcome events. The QoR-15 and WHODAS questionnaires were repeated on day 30,[23] and the WHODAS questionnaire was repeated at 3 months, 6 months, and 12 months after surgery to ascertain survival status and new-onset disability. Source documentation was required to confirm the occurrence of surgical-site infection, pneumonia, or other septic complications up to 30 days after surgery; renal-replacement therapy up to 90 days; and death during the first year (see the Supplementary Appendix).

TRIAL OUTCOMES

The primary outcome was disability-free survival up to 1 year after surgery. Disability was defined as a persistent impairment in health status (lasting ≥6 months), as measured by a score of at least 24 points on the WHODAS questionnaire, which reflects a disability level of at least 25% (the threshold point between "disabled" and "not disabled").[23,27] The WHODAS questionnaire was completed by the patient or by a proxy (a spouse or caregiver) if the patient was not able to complete it. The date of onset of any new disability was recorded (see the Supplementary Appendix).

The secondary outcomes were acute kidney injury, a composite of 30-day mortality or major septic complications (sepsis, surgical-site infection, anastomotic leak, or pneumonia), serum lactate level (at 6 and 24 hours), peak C-reactive protein level, blood transfusion, duration of stay in the intensive care unit (ICU) and hospital, unplanned admission to the ICU, and quality of recovery. Acute kidney injury was defined according to the criteria of the Kidney Disease: Improving Global Outcomes group, on a scale of 1 to 3, with higher values indicating increased severity.[28] We also recorded the incidence of renal-replacement therapy up to day 90. We adjusted creatinine measurements on day 1 and day 3 according to the patient's fluid balance at 1 day and 3 days after surgery (see the Supplementary Appendix).[22,29]

STATISTICAL ANALYSIS

We performed all the analyses in a modified intention-to-treat population, which included all the patients who had undergone both randomization and induction of general anesthesia for eligible surgery. All the patients were followed for the duration of the trial, unless they withdrew consent. In the latter case, data were censored at the time that consent was withdrawn.

With an expected probability of 1-year disability-free survival of 65%[30,31] and a type I error of 0.05, we calculated that the enrollment of 2650 patients (with 850 events of death or disability) was required to provide a power of 90% to detect a hazard ratio of 0.80 using the log-rank test. The sample size was inflated to 2800 patients to account for withdrawals and loss to follow-up. The steering committee met on June 30, 2016, to discuss the results of a review by the data-quality committee and the accruing incidence of disability. With the randomization of 2578 patients (1443 with complete follow-up), 300 primary outcome events had occurred, with a greater-than-expected probability of 1-year disability-free survival of 85%. We

therefore increased the sample size to 3000 (with ≥380 events) to provide a power of 80% to detect a hazard ratio of 0.75. In actuality, 533 events were observed in the trial (event-free rate, 82%), which provided a power of 80% to detect a hazard ratio of 0.78.

We used the Kaplan–Meier method to calculate the probability of the primary outcome. Hazard ratios for the time until the occurrence of disability or death between the two groups were estimated with the use of a Cox proportional-hazards model, in which data for patients without an event were censored at the date of the last contact, with assessment of proportionality of hazards based on Schoenfeld residuals testing (see the Supplementary Appendix). Analyses of the time until death or a new onset of disability were performed similarly.

For outcomes that were measured on a binary scale, we used log-binomial regression to estimate risk ratios directly or exact logistic regression to approximate these values if the number of events in either group was fewer than 10. In the analyses of end points regarding acute kidney injury, we used multiply imputed fluid-balance measurements if such values were missing (see the Supplementary Appendix). Outcomes regarding the duration and length of hospital stay in the two groups were compared with the use of the Wilcoxon–Breslow–Gehan test, with data censored at 30 days and in-hospital deaths assigned the longest duration of stay. Continuous outcomes were analyzed with the use of linear regression with robust standard errors; these were first log-transformed if the values were right-skewed, or median regression was used if the values were left-skewed. A post hoc procedure to control for multiple testing was applied to all secondary outcomes with the use of the Holm–Bonferroni method,[32] with a family-wise significance level of 0.049 to account for the interim analysis. Sensitivity analyses with respect to missing data are provided in the Supplementary Appendix.

Data for patients were analyzed in subgroups that included sex, age quartile, location of trial center (country), presence or absence of colorectal surgery, and use or nonuse of a goal-directed device. Analyses of heterogeneity of effects across subgroups were performed with the use of treatment-by-covariate terms added to the Cox regression models.

Results

PATIENT ENROLLMENT AND FOLLOW-UP

Table 1.

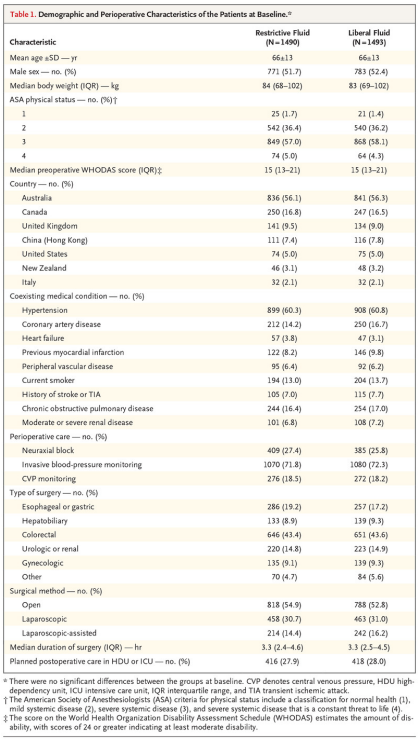


Table 1. Demographic and Perioperative Characteristics of the Patients at Baseline.*

Characteristic	Restrictive Fluid (N = 1490)	Liberal Fluid (N = 1493)
Mean age ±SD — yr	66±13	66±13
Male sex — no. (%)	771 (51.7)	783 (52.4)
Median body weight (IQR) — kg	84 (68–102)	83 (69–102)
ASA physical status — no. (%)†		
1	25 (1.7)	21 (1.4)
2	542 (36.4)	540 (36.2)
3	849 (57.0)	868 (58.1)
4	74 (5.0)	64 (4.3)
Median preoperative WHODAS score (IQR)‡	15 (13–21)	15 (13–21)
Country — no. (%)		
Australia	836 (56.1)	841 (56.3)
Canada	250 (16.8)	247 (16.5)
United Kingdom	141 (9.5)	134 (9.0)
China (Hong Kong)	111 (7.4)	116 (7.8)
United States	74 (5.0)	75 (5.0)
New Zealand	46 (3.1)	48 (3.2)
Italy	32 (2.1)	32 (2.1)
Coexisting medical condition — no. (%)		
Hypertension	899 (60.3)	908 (60.8)
Coronary artery disease	212 (14.2)	250 (16.7)
Heart failure	57 (3.8)	47 (3.1)
Previous myocardial infarction	122 (8.2)	146 (9.8)
Peripheral vascular disease	95 (6.4)	92 (6.2)
Current smoker	194 (13.0)	204 (13.7)
History of stroke or TIA	105 (7.0)	115 (7.7)
Chronic obstructive pulmonary disease	244 (16.4)	254 (17.0)
Moderate or severe renal disease	101 (6.8)	108 (7.2)
Perioperative care — no. (%)		
Neuraxial block	409 (27.4)	385 (25.8)
Invasive blood-pressure monitoring	1070 (71.8)	1080 (72.3)
CVP monitoring	276 (18.5)	272 (18.2)
Type of surgery — no. (%)		
Esophageal or gastric	286 (19.2)	257 (17.2)
Hepatobiliary	133 (8.9)	139 (9.3)
Colorectal	646 (43.4)	651 (43.6)
Urologic or renal	220 (14.8)	223 (14.9)
Gynecologic	135 (9.1)	139 (9.3)
Other	70 (4.7)	84 (5.6)
Surgical method — no. (%)		
Open	818 (54.9)	788 (52.8)
Laparoscopic	458 (30.7)	463 (31.0)
Laparoscopic-assisted	214 (14.4)	242 (16.2)
Median duration of surgery (IQR) — hr	3.3 (2.4–4.6)	3.3 (2.5–4.5)
Planned postoperative care in HDU or ICU — no. (%)	416 (27.9)	418 (28.0)

* There were no significant differences between the groups at baseline. CVP denotes central venous pressure, HDU high-dependency unit, ICU intensive care unit, IQR interquartile range, and TIA transient ischemic attack.
† The American Society of Anesthesiologists (ASA) criteria for physical status include a classification for normal health (1), mild systemic disease (2), severe systemic disease (3), and severe systemic disease that is a constant threat to life (4).
‡ The score on the World Health Organization Disability Assessment Schedule (WHODAS) estimates the amount of disability, with scores of 24 or greater indicating at least moderate disability.

Demographic and Perioperative Characteristics of the Patients at Baseline.

From May 2013 through September 2016, a total of 5223 patients met the eligibility requirements for enrollment at 47 centers in seven countries. Of these patients, we randomly assigned 3000 patients to a restrictive fluid regimen (1501 patients) or a liberal fluid regimen (1499 patients) (Table S1 and Fig. S1 in the Supplementary Appendix). Of these patients, 2983 (99.4%) met the inclusion criteria for the modified intention-to-treat population (1490 in the restrictive fluid group and 1493 in the liberal fluid group). The mean number of patients per site was 64 (range, 1 to 227). The mean age was 66 years, 43% underwent colorectal surgery, and 64% underwent cancer surgery. There were no significant differences between the groups at baseline (Table 1, and Table S2 in the Supplementary Appendix). Among the patients who had undergone randomization, 1-year outcome data were available for 2901 (96.7%) (Table 1, and Fig. S1 in the Supplementary Appendix).

TRIAL TREATMENT

Table 2.

Table 2. Blood Loss and Administered Intravenous-Fluid Volumes.*

Variable	Restrictive Fluid (N=1490)	Liberal Fluid (N=1493)	P Value
During surgery			
Median intraoperative blood loss (IQR) — ml	200 (100 to 400)	200 (100 to 500)	0.14†
Median intraoperative fluid administration (IQR) — ml			
Crystalloid	1677 (1173 to 2294)	3000 (2100 to 3850)	<0.001
Colloid‡	500 (250 to 800)	500 (400 to 1000)	0.01
Median infusion rate (IQR) — ml/kg/hr	6.5 (5.1 to 8.4)	10.9 (8.7 to 13.5)	<0.001
In PACU§			
Median administration of fluid (IQR) — ml			
Crystalloid	160 (90 to 302)	300 (160 to 500)	<0.001
Colloid‡	400 (250 to 500)	500 (250 to 500)	0.27
Postoperative day 1, post-PACU			
Median administration of fluid (IQR) — ml			
Crystalloid	1556 (1200 to 1960)	2600 (2052 to 3150)	<0.001
Colloid‡	500 (250 to 1000)	500 (400 to 750)	0.89
Median infusion rate (IQR) — ml/kg/hr	0.9 (0.7 to 1.2)	1.5 (1.2 to 1.7)	<0.001
At 24 hr after surgery			
Median cumulative total for intravenous fluids (IQR) — ml	3671 (2885 to 4880)	6146 (5000 to 7410)	<0.001
Median fluid balance (IQR) — ml¶	1380 (540 to 2338)	3092 (2010 to 4241)	<0.001†
Median weight gain (IQR) — kg‖	0.3 (−1.0 to 1.9)	1.6 (0.0 to 3.6)	ND

* ND denotes not done, and PACU postanesthesia care unit.
† This P value was calculated from 10 imputations of missing values.
‡ Colloid was administered during the perioperative period in 369 patients in the restrictive fluid group and 309 patients in the liberal fluid group (P=0.008); in the PACU in 130 patients and 92 patients, respectively (P=0.006); and on postoperative day 1 after leaving the PACU in 207 patients and 127 patients, respectively (P<0.001).
§ Patients who bypassed the PACU and were admitted directly to the ICU or HDU included 116 in the restrictive fluid group and 106 in the liberal fluid group.
¶ Data regarding fluid balance were missing for 179 patients in the restrictive fluid group and 161 in the liberal fluid group. Results were not meaningfully different after multiple imputation.
‖ Data regarding weight gain were missing for 1036 patients in the restrictive fluid group and 999 in the liberal fluid group; the P value was not calculated.

Blood Loss and Administered Intravenous-Fluid Volumes.

The volumes of fluids that were administered to patients in each group are presented in Table 2, and in Tables S3 to S5 in the Supplementary Appendix. During surgery, the median rate of fluid infusion was 6.5 ml per kilogram per hour (interquartile range, 5.1 to 8.4) in the restrictive fluid group and 10.9 ml per kilogram per hour (interquartile range, 8.7 to 13.5) in the liberal fluid group. On postoperative day 1, the median rate of fluid infusion was 0.9 ml per kilogram per hour (interquartile range, 0.7 to 1.2) in the restrictive fluid group and 1.5 ml per kilogram per hour (interquartile range, 1.2 to 1.7) in the liberal fluid group.

Selected ERAS elements that were aimed at improving outcomes were not clinically different across groups (Table S6 in the Supplementary Appendix). Patients in the restrictive fluid group were more likely than those in the liberal fluid group to receive vasopressor support (P=0.02), have lower urine output (P<0.001), and have a higher incidence of oliguria or anuria (P<0.001) but were less likely to require red-cell transfusion (P=0.02) or gain weight during the first 2 days after surgery (Table S7 in the Supplementary Appendix).

PRIMARY OUTCOME

Table 3.

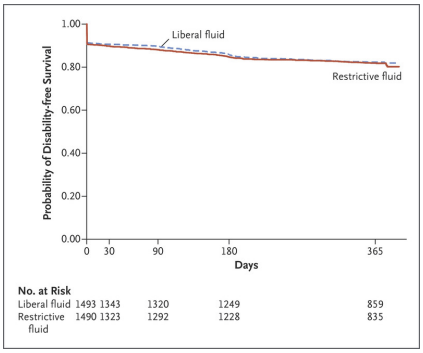
Table 3. Primary and Secondary Outcomes.*

Outcome	Restrictive Fluid (N = 1490)	Liberal Fluid (N = 1493)	Hazard or Risk Ratio (95% CI)†	P Value
Primary outcome				
Disability-free survival at 1 yr — no. (%)‡	1223 (81.9)	1232 (82.3)	1.05 (0.88–1.24)	0.61
Death or persistent disability — no.	267	261		
Death	95	96		
Persistent disability	172	165		
Secondary outcomes§				
Composite septic outcome or death — no./total no. (%)¶	323/1481 (21.8)	295/1487 (19.8)	1.10 (0.96–1.27)	0.19
Surgical-site infection — no./total no. (%)	245/1481 (16.5)	202/1487 (13.6)	1.22 (1.03–1.45)	0.02‖
Sepsis — no./total no. (%)	157/1481 (10.6)	129/1487 (8.7)	1.22 (0.98–1.52)	0.08
Anastomotic leak — no./total no. (%)	49/1481 (3.3)	35/1487 (2.4)	1.41 (0.92–2.16)	0.12
Pneumonia — no./total no. (%)	54/1481 (3.6)	57/1487 (3.8)	0.95 (0.66–1.37)	0.79
Acute kidney injury — no./total no. (%)**	124/1443 (8.6)	72/1439 (5.0)	1.71 (1.29–2.27)	<0.001
Renal-replacement therapy — no./total no. (%)	13/1460 (0.9)	4/1462 (0.3)	3.27 (1.01–13.8)	0.048‖
Pulmonary edema — no./total no. (%)	20/1481 (1.4)	32/1487 (2.2)	0.63 (0.36–1.09)	0.10
Unplanned admission to ICU — no./total no. (%)	161/1487 (10.8)	145/1491 (9.7)	1.11 (0.90–1.38)	0.32
Median peak serum lactate level (IQR) — mmol per liter††	1.6 (1.1–2.5)	1.6 (1.1–2.4)	NA	NA
Median C-reactive protein level on day 3 (IQR) — mg per liter‡‡	136 (82–198)	133 (80–200)	NA	0.66
Median duration of mechanical ventilation (IQR) — hr§§	17 (5–65)	14 (3–31)	NA	0.07
Median score on quality-of-recovery scale (IQR)¶¶	106 (89–121)	107 (90–122)	NA	0.31
Median duration of stay in HDU or ICU (IQR) — days‖‖	1.8 (1.0–3.1)	1.4 (0.9–2.9)	NA	0.13
Median duration of hospital stay (IQR) — days	6.4 (3.6–10.6)	5.6 (3.6–10.5)	NA	0.26
Death — no. (%)‡				
At 90 days	31 (2.1)	18 (1.2)	1.73 (0.97–3.10)	0.06
At 12 mo	95 (6.5)	96 (6.6)	1.03 (0.78–1.36)	0.86

* NA denotes not applicable.
† The hazard ratio or risk ratio is for the restrictive fluid group as compared with the liberal fluid group.
‡ Percentages in this category were estimated with the use of the Kaplan–Meier method. Among the patients who died, 9 in the restrictive fluid group and 12 in the liberal fluid group had persistent disability before death at 12 months. The risks of death at 90 days and at 12 months are listed in the table as predefined secondary outcomes.
§ All the secondary outcomes were assessed up to 30 days after surgery, with the exception of renal-replacement therapy and the duration of mechanical ventilation, which were assessed at 90 days.
¶ The composite septic outcome includes surgical-site infection, anastomotic leak, pneumonia, and sepsis.
‖ The *P* value was not significant after adjustment for multiple comparisons, with a threshold level of P=0.004 for renal-replacement therapy and P=0.003 for surgical-site infection.
** Values for acute kidney injury are the average number of events across 10 imputations in which fluid balance was imputed after adjustment for serum creatinine values on day 1 and day 3. Details regarding these analyses and sensitivity analyses are provided in the Supplementary Appendix.
†† Data regarding the peak serum lactate level were missing for 1057 patients in the restrictive fluid group and in 1086 in the liberal fluid group; the P value was not calculated.
‡‡ Data regarding the C-reactive protein level were missing for 422 patients in the restrictive fluid group and 420 in the liberal fluid group.
§§ Data regarding mechanical ventilation are for 102 patients in the restrictive fluid group and 100 in the liberal fluid group.
¶¶ Data regarding the quality of recovery on day 3 were missing for 73 patients in the restrictive fluid group and 75 in the liberal fluid group. The scores on this scale range from 0 (extremely poor) to 150 (excellent).
‖‖ Data regarding the duration of stay in the HDU or ICU data are for 485 patients in the restrictive fluid group and 473 in the liberal fluid group who were admitted at any time postoperatively.

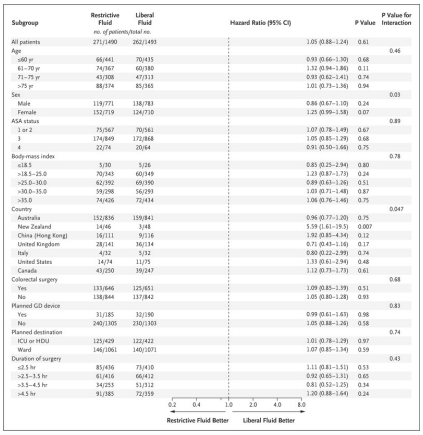
Primary and Secondary Outcomes.

Figure 1.



Probability of Freedom from Death or Persistent Disability 1 Year after Surgery.

Figure 2.



Hazard Ratios for Death or Disability in Prespecified Subgroups.

The median follow-up time was 366 days in each group. The rate of disability-free survival at 1 year was 81.9% in the restrictive fluid group and 82.3% in the liberal fluid group (hazard ratio for death or disability,

1.05; 95% confidence interval, 0.88 to 1.24; P=0.61) (Table 3 and Figure 1, and Fig. S2 in the Supplementary Appendix). Death or persistent disability occurred in 267 patients (95 deaths and 172 cases of persistent disability) in the restrictive fluid group and in 261 patients (96 deaths and 165 cases of persistent disability) in the liberal fluid group. The effect of restrictive fluid therapy on the risk of disability-free survival was consistent across subgroups, including planned use of a goal-directed device (P=0.37), with the exception of sex and country, including a significant between-group difference among residents of New Zealand (Figure 2). The distributions of baseline variables in female patients and residents of New Zealand are provided in Tables S8 and S9 in the Supplementary Appendix, respectively.

SECONDARY OUTCOMES

Acute kidney injury occurred in 124 patients (8.6%) in the restrictive fluid group and in 72 patients (5.0%) in the liberal fluid group (P<0.001), as calculated from the average of 10 multiply imputed data sets (Table 3). Renal-replacement therapy was performed in 13 patients (0.9%) and 4 patients (0.3%), respectively (unadjusted P=0.048; threshold level for statistical significance after adjustment for multiple comparisons, P=0.004) (Table 3, and Table S12 in the Supplementary Appendix). The risk of acute kidney injury was largely unaffected by the assigned treatment if postoperative creatinine values were not adjusted according to fluid balance or with the use of additional methods to account for missing data (Tables S10 and S11 in the Supplementary Appendix).

Septic complications or death up to 30 days after surgery occurred in 323 patients (21.8%) in the restrictive fluid group and 295 patients (19.8%) in the liberal fluid group (P=0.19). Surgical-site infection occurred in 245 patients (16.5%) in the restrictive fluid group and in 202 patients (13.6%) in the liberal fluid group (unadjusted P=0.02; threshold level for statistical significance after adjustment for multiple comparisons, P=0.003) (Table 3, and Table S12 in the Supplementary Appendix). There were no other significant between-group differences in the rates of trial outcomes (Table 3, and Tables S6 and S13 in the Supplementary Appendix).

SENSITIVITY ANALYSES

In sensitivity analyses, the proportion of patients who were alive and free of new-onset disability at 1 year was 81.4% in the restrictive fluid group and 83.3% in the liberal fluid group (P=0.13 by Cox regression); modifications to the disability definition did not meaningfully change the results (Tables S14 and S15 and Figs. S3 and S4 in the Supplementary Appendix). Results were largely unchanged after adjustment for stratification factors that were used in randomization (Tables S16 and S17 in the Supplementary Appendix).

Discussion

In this international trial evaluating disability-free survival and rates of serious complications among at-risk patients undergoing major abdominal surgery, we compared a restrictive regimen for the administration of intravenous fluid (designed to achieve zero balance during surgery and the 24-hour postoperative period)

with a liberal fluid regimen. At 1 year, the rate of disability-free survival was not significantly higher with the restrictive fluid regimen than with the liberal fluid regimen. However, patients in the restrictive fluid group had a significantly higher risk of acute kidney injury than those in the liberal fluid group.

Perioperative intravenous-fluid therapy serves to restore and maintain body water, electrolytes, and organ perfusion to achieve homeostasis.[14,33] Avoiding too much intravenous fluid is commonly recommended in ERAS programs.[12,14,16,33,34] Some small trials have supported a restrictive fluid regimen.[9,11,13] However, inappropriate fluid-balance approaches can be harmful.[24,35] In particular, acute kidney injury may result from inadequate administration of fluid (renal hypoperfusion)[28] or excessive administration (renal interstitial edema).[19] Our findings may resolve this uncertainty, since we found that restricting intravenous-fluid administration with the aim of zero balance increased the risk of acute kidney injury.

Intravenous-fluid regimens for abdominal surgery have been classified as restrictive (<1.75 liters per day), balanced (1.75 to 2.75 liters per day), and liberal (>2.75 liters per day).[33] In our trial, the patients who were assigned to the restrictive fluid group received a median of 1.7 liters intraoperatively and an additional 1.9 liters during the 24-hour postoperative period. Patients in the liberal fluid group received 3.0 liters during surgery and an additional 3.0 liters during the first 24 hours (similar to the amount recorded in registry data[24] and pooled analyses of trials).[10,25] In previous studies, intraoperative restrictive fluid replacement varied from 1.0 to 2.7 liters, as compared with 2.8 to 5.4 liters in liberal fluid regimens.[34] Current recommendations suggest avoiding a weight gain of more than 2.5 kg,[14,16] a cutoff that was achieved in a majority of the patients in our trial, including those in the liberal fluid group.

Our findings should not be used to support excessive administration of intravenous fluid. Rather, they show that a regimen that includes a modestly liberal administration of fluid is safer than a restrictive regimen. There is a belief that fluid-induced edema impairs wound healing. In contrast, we identified a higher rate of surgical-site infection in the restrictive fluid group, possibly because of wound or anastomotic hypoperfusion. Fluid restriction will inevitably increase the need for vasopressor therapy unless hypotension is ignored.

Our trial has certain limitations. Obviously, clinicians could not administer intravenous fluids in a blinded manner. This lack of blinding may have introduced bias in documentation and some outcome monitoring. The trial was pragmatic and included a range of abdominal surgeries with an aim toward generalizability. Less than half of the patients were treated according to ERAS principles, a factor that did not influence the overall effects of the fluid intervention. The trial dictated the administration of fluid therapy during and for the first 24 hours after surgery, when most intravenous fluid is given; however, the administration of later fluid therapy was not controlled. Many patients could not be weighed on days 1 to 3. We identified a lower risk of disability-free survival in the restrictive fluid group among patients in New Zealand. This secondary finding was based on a small number of events and cannot be explained by baseline imbalance, so it may be spurious. Some of the results for secondary outcomes may be spurious because of an alpha-level error. However, the risk of acute kidney injury in the restrictive fluid group was highly significant and was coherent in the context of oliguria and the use of renal-replacement therapy.

In conclusion, in patients at increased risk for complications while undergoing major abdominal surgery, a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen 1 year after surgery. However, the restrictive regimen was associated with a higher rate of acute kidney injury.

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Disclosure forms provided by the authors are available at NEJM.org.

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A list of participating centers and investigators in the RELIEF trial is provided in the Supplementary Appendix, available at NEJM.org.

Supplementary Material

Protocol	PDF	1471KB
Supplementary Appendix	PDF	2068KB
Disclosure Forms	PDF	265KB

References (35)

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. Lancet 2015;385:Suppl 2:S11-S11.
Crossref Web of Science Medline Google Scholar

2. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg 1961;154:803-810.
Crossref Web of Science Medline Google Scholar

3. Arkiliç CF, Taguchi A, Sharma N, et al. Supplemental perioperative fluid administration increases tissue oxygen pressure. Surgery 2003;133:49-55.
Crossref Medline Google Scholar

4. Mythen MG, Webb AR. The role of gut mucosal hypoperfusion in the pathogenesis of post-operative organ dysfunction. Intensive Care Med 1994;20:203-209.
Crossref Medline Google Scholar

5. Davies SJ, Wilson RJ. Preoperative optimization of the high-risk surgical patient. Br J Anaesth 2004;93:121-128.
Crossref Web of Science Medline Google Scholar

6. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 1993;270:2699-2707.
Crossref Web of Science Medline Google Scholar

7. Wilson J, Woods I, Fawcett J, et al. Reducing the risk of major elective surgery: randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 1999;318:1099-1103.
Crossref Web of Science Medline Google Scholar

8. Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. World J Surg 2004;28:1046-1051.
Crossref Medline Google Scholar

9. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg 2003;238:641-648.
Crossref Web of Science Medline Google Scholar

10. Boland MR, Noorani A, Varty K, Coffey JC, Agha R, Walsh SR. Perioperative fluid restriction in major abdominal surgery: systematic review and meta-analysis of randomized, clinical trials. World J Surg 2013;37:1193-1202.
Crossref Medline Google Scholar

11. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet 2002;359:1812-1818.
Crossref Web of Science Medline Google Scholar

12. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS) Society recommendations. Clin Nutr 2012;31:783-800.
Crossref Medline Google Scholar

13. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 2005;103:25-32.
Crossref Web of Science Medline Google Scholar

14. Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand 2016;60:289-334.
Crossref Medline Google Scholar

15. Intravenous fluid therapy in adults in hospital: clinical guideline CG174. London: National Institute for Health and Care Excellence, 2017 (https://www.nice.org.uk/guidance/cg174).
Google Scholar

16. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: a review. JAMA Surg 2017;152:292-298.
Crossref Medline Google Scholar

17. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. Anesth Analg 2012;114:640-651.
Crossref Web of Science Medline Google Scholar

18. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. Chest 1999;115:1371-1377.
Crossref Medline Google Scholar

19. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. Nat Rev Nephrol 2010;6:107-115.
Crossref Medline Google Scholar

20. Ratner AJ, Lysenko ES, Paul MN, Weiser JN. Synergistic proinflammatory responses induced by polymicrobial colonization of epithelial surfaces. Proc Natl Acad Sci U S A 2005;102:3429-3434.
Crossref Medline Google Scholar

21. Lang K, Boldt J, Suttner S, Haisch G. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. Anesth Analg 2001;93:405-409.
Medline Google Scholar

22. Myles P, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy in major abdominal surgery (RELIEF): rationale and design for a multicentre randomised trial. BMJ Open 2017;7(3):e015358-e015358.
Crossref Medline Google Scholar

23. World report on disability: technical appendix C. Geneva: World Health Organization, 2011:287-94 (http://www.who.int/disabilities/world_report/2011/report.pdf).
Google Scholar

24. Thacker JK, Mountford WK, Ernst FR, Krukas MR, Mythen MM. Perioperative fluid utilization variability and association with outcomes: considerations for enhanced recovery efforts in sample US surgical populations. Ann Surg 2016;263:502-510.
Crossref Medline Google Scholar

25. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br J Surg 2009;96:331-341.
Crossref Medline Google Scholar

26. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. Anesthesiology 2013;118:1332-1340.
Crossref Web of Science Medline Google Scholar

27. Shulman MA, Myles PS, Chan MT, McIlroy DR, Wallace S, Ponsford J. Measurement of disability-free survival after surgery. Anesthesiology 2015;122:524-536.
Crossref Medline Google Scholar

28. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary. Crit Care 2013;17:204-204.
Crossref Web of Science Medline Google Scholar

29. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med 2011;39:2665-2671.
Crossref Medline Google Scholar

30. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JR, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: randomised trial. BMJ 2011;342:d1491-d1491.
Crossref Medline Google Scholar

31. Mamidanna R, Burns EM, Bottle A, et al. Reduced risk of medical morbidity and mortality in patients selected for laparoscopic colorectal resection in England: a population-based study. Arch Surg 2012;147:219-227.
Crossref Medline Google Scholar

32. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65-70.
Web of Science Google Scholar

33. Varadhan KK, Lobo DN. A meta-analysis of randomised controlled trials of intravenous fluid therapy in major elective open abdominal surgery: getting the balance right. Proc Nutr Soc 2010;69:488-498.
Crossref Web of Science Medline Google Scholar

34. Bundgaard-Nielsen M, Secher NH, Kehlet H. 'Liberal' vs. 'restrictive' perioperative fluid therapy — a critical assessment of the evidence. Acta Anaesthesiol Scand 2009;53:843-851.
Crossref Medline Google Scholar

35. Bellamy MC. Wet, dry or something else? Br J Anaesth 2006;97:755-757.
Crossref Medline Google Scholar

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Clinical Practice

CLINICAL PRACTICE

Fluids, vasopressors, and acute kidney injury after major abdominal surgery between 2015 and 2019: a multicentre retrospective analysis

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Abstract

Background: Practice patterns related to intraoperative fluid administration and vasopressor use have potentially evolved over recent years. However, the extent of such changes and their association with perioperative outcomes, such as the development of acute kidney injury (AKI), have not been studied.

Methods: We performed a retrospective analysis of major abdominal surgeries in adults across 26 US hospitals between 2015 and 2019. The primary outcome was AKI as defined by the Kidney Disease Improving Global Outcomes definition (KDIGO) using only serum creatinine criteria. Univariable linear predictive additive models were used to describe the dose-dependent risk of AKI given fluid administration or vasopressor use.

Results: Over the study period, we observed a decrease in the volume of crystalloid administered, a decrease in the proportion of patients receiving more than 10 ml kg^{-1} h^{-1} of crystalloid, an increase in the amount of norepinephrine equivalents administered, and a decreased duration of hypotension. The incidence of AKI increased between 2016 and 2019. An increase of crystalloid administration from 1 to 10 ml kg^{-1} h^{-1} was associated with a 58% decreased risk of AKI.

Conclusions: Despite decreased duration of hypotension during the study period, decreased fluid administration and increased vasopressor use were associated with increased incidence of AKI. Crystalloid administration below 10 ml kg^{-1} h^{-1} was associated with an increased risk of AKI. Although no causality can be concluded, these data suggest that prevention and treatment of hypotension during abdominal surgery with liberal use of vasopressors at the expense of fluid administration is associated with an increased risk of postoperative AKI.

Keywords: acute kidney injury; fluid therapy; hypotension; major abdominal surgery; vasopressor

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Editor's key points

- Whilst inadequate intravenous fluid administration has been associated with kidney injury, so has excessive intravenous fluid administration.
- A general move towards more restrictive fluids for surgery may have led to an increased risk of kidney injury.
- This real-world study investigates two components of hypotension management (fluids, vasopressors) and links these with postoperative kidney injury.
- A more restrictive perioperative fluid regimen is associated with postoperative kidney injury and could be harmful to the kidneys.

Fluid administration and use of vasopressors are key treatments for maintenance of haemodynamics. However, recommendations for perioperative fluid administration have evolved over the past decade from liberal (5 L given on the day of surgery), to restrictive, with a target of net zero balance.[1–3]

Because the kidneys are particularly susceptible to injury from intraoperative haemodynamic changes, measurement of postoperative acute kidney injury (AKI) represents a major endpoint for intraoperative haemodynamic optimisation.[4,5] The effect of fluid or vasopressor use, and other practice changes on the development of AKI in the surgical setting remains poorly understood.[6–9]

In this multicentre retrospective observational study, we describe the 5-yr trend of fluid administration and vasopressor use among different Multicenter Perioperative Outcomes Group (MPOG) institutions in patients undergoing elective abdominal surgery requiring general anaesthesia and their associations with postoperative AKI. We hypothesised that (1) there exist temporal changes in practice with more restrictive fluid administration and more liberal vasopressor use, and that (2) these practices are associated with a risk of developing postoperative AKI.

Methods

Approval for a retrospective review of electronic medical records was obtained by our institution's Institutional Review Board (IRB# 19–269641), and the requirement for written informed consent was waived. Study outcomes, data collection, and statistical methods were established *a priori*, presented, and approved by the MPOG peer-review forum before data analysis.[10] The REporting of studies Conducted using Observational Routinely collected health data (RECORD) statement was followed throughout this study.

Data were extracted from the MPOG database, a research consortium of 56 hospitals across the USA and Europe. Hospitals with a medical school affiliation are classified as academic.[11] Methods used for data input, storage, quality assurance, and extraction within the MPOG consortium have been described elsewhere[12] and utilised in prior studies.[13,14]

Study population

We included patients >18 yr undergoing non-emergent, non-obstetric, and non-ambulatory major abdominal surgery, as determined by a combination of anaesthesia Current Procedural Terminology (CPT) code and procedure name (Supplementary Methods), with a case duration >120 min, requiring general anaesthesia, between January 1, 2015, and January 1, 2020 (Supplementary Fig. S1). Patients undergoing surgery after 2020 were not included to avoid impact of the COVID-19 pandemic on surgical volume and outcomes.[15,16] Institutions must have been participating in and contributing to MPOG data collection for the entirety of the study period to be included. Patients had at least one preoperative creatinine and one postoperative creatinine measurement within 7 days of surgery to assess for AKI. Exclusion criteria included liver resections, organ transplantations, patients requiring intraoperative bolus or infusion of select inotropes and vasopressors (dobutamine, dopamine, epinephrine, isoproterenol, milrinone, and vasopressin), patients receiving vasopressors before induction of anaesthesia, patients intubated before induction of anaesthesia, and ASA class 5 and 6. Patients with missing values in critical variables (e.g. case duration, weight) were also excluded. A minimum sample size of 14 000 patients was determined to detect a 1% change in an estimated rate AKI at 10% (two-sided).

Data preprocessing

Data were preprocessed in Python 3 (CreateSpace, Scotts Valley, CA, USA).[17] Based on the distribution, continuous variables with values greater than three standard deviations of the mean were replaced with missing values. Missing values were permitted in univariable analysis. Only complete cases were used in multivariable analysis. Total crystalloid use was defined as the sum of normal saline and balanced crystalloid solutions (Lactated Ringer's and PlasmaLyte). In 4899 cases, individual crystalloid values were not available, and a predefined MPOG variable was substituted. This variable is available for all patients and represents total use of crystalloids including certain dextrose-containing solutions.[18] Total crystalloid and albumin administration was summated in a 1:1 ratio. Blood products were not considered as i.v. fluids. Norepinephrine and phenylephrine doses (bolus and infusion) were converted to norepinephrine equivalents using the following equation: norepinephrine equivalents=[norepinephrine (μg kg^{-1})]+[phenylephrine (μg kg^{-1})÷10].[19] Ephedrine was not included because of its bolus administration and variable physiological effect as an indirect sympathomimetic agonist. Nephrotoxic medications (NSAIDs and vancomycin) were chosen based on their common use in surgical patients.[20] I.V. contrast was not considered as a nephrotoxic agent because its toxicity in the kidney has been controversial.[21]

Statistical analysis

Descriptive statistics were performed using the software R (R Foundation for Statistical Computing, Vienna, Austria).[22] Baseline differences for continuous variables were tested with the analysis of variance (ANOVA) or Kruskal–Wallis test and the χ^2 test for categorical variables. The Jonckheere–Terpstra test was used to assess for monotonic trends over the study period for total crystalloid and vasopressor use.[23] The primary outcome was AKI as defined by the Kidney Disease-Improving Global Outcomes definition (KDIGO) using serum creatinine criteria. Secondary outcomes were mortality within 30 days of procedure and severe AKI (KDIGO stage 2 or 3). To describe the odds of developing AKI, we developed a mixed-effects multivariable logistic regression model with fixed variables (Supplementary Methods) based on previously reported risk factors for AKI and institution as a random effect.[24] We described the odds of mortality in a separate model with the same variables. We developed general additive models (R packages 'oddsratio',

'mgcv') using spline transformation, a Poisson approach with robust error variances,[25] and institution as a random effect to describe risk of any stage of AKI with administration of crystalloids ranging from 1 to 10 ml kg^{-1} h^{-1} and use of norepinephrine equivalents ranging from 0 to 0.04 μg kg^{-1} min^{-1}. Predefined subgroup analyses of risk included patients >65 yr, hypertension, ASA Class, history of heart failure (congestive heart failure [CHF]), and history of chronic kidney disease (CKD).

Results

Population characteristics

Among the 281 010 patients with records during the study period, 32 250 patients (11.4%) were included from 17 academic and 9 non-academic institutions (Supplementary Fig. S1). The mean age was 58 yr, 52.2% of patients were female, and the majority of patients were classified with an ASA class of 3 or 4 (62.1%) (Supplementary Table S1). The most frequent comorbidities included hypertension (49.4%), diabetes (16.2%), and chronic obstructive pulmonary disease (COPD) (14.9%). AKI occurred in 12.4%, and 30-day mortality in 0.3%. From 2015 to 2019, there was an increase in patient age, female patients, patient illness severity (i.e. ASA class 3 or 4 patients, or presence of comorbidities), and duration of surgical cases (Table 1, Supplementary Table S2).

Temporal trends: use of intravenous fluids

Over the study period, the volume of crystalloids administered decreased from 6.4 (4.3) ml kg^{-1} h^{-1} to 5.5 (3.8) ml kg^{-1} h^{-1} ($P<0.001$, Fig. 1a). Although the proportion of patients receiving albumin increased between 2015 and 2019 (16% *vs* 20%, $P<0.001$), the volume of albumin administered remained the same, resulting in a net decrease in total volume of crystalloid and colloids administered between 2015 and 2018 (Fig. 1d and e). The proportion of patients receiving <10 ml kg^{-1} h^{-1} of crystalloid ranged from 82% to 90%, with a nadir in 2018 ($P<0.001$, Table 1). Total crystalloid use was stratified by institution (Supplementary Fig. S2A) and anaesthetic CPT code (Supplementary Figure S3A).

Temporal trends: use of vasopressors

Vasopressor use increased from 2015 to 2019 with norepinephrine equivalents increasing from 0.003 (0.009) μg kg^{-1} min^{-1} to 0.006 (0.03) μg kg^{-1} min^{-1} ($P<0.001$, Fig. 2a). Phenylephrine use increased accordingly, whereas the use of norepinephrine increased after 2018 (Fig. 2b and c). The proportion of patients who received a vasopressor infusion increased from 14% to 27% during the study period. The proportion of patients who required no vasopressors decreased from 47% to 38% ($P<0.001$, Table 1). Total vasopressor use was stratified by institution (Supplementary Fig. S2B) and by anaesthetic CPT (Supplementary Fig. S3B).

We observed an increase in vasopressor infusion requirement in patients who received less than 10 ml kg^{-1} h^{-1} of crystalloid, from 10.6% to 23.7% ($P<0.001$, Table 1). In patients who received more than 10 ml kg^{-1} h^{-1} of crystalloid, the vasopressor infusion requirement did not change.

Temporal trends: duration of hypotension

The total duration of hypotension, defined as MAP <65 mm Hg, was highest in 2016 at 25 (36) min and lowest in 2019 at 23 (29) min ($P<0.001$, Table 1).

Temporal trends in the development of acute kidney injury and associated factors

The incidence of postoperative AKI was the highest in 2015 (13.5%), decreased in 2016 (11.4%) and 2017 (11.7%), and increased in 2018 (12.4%) and 2019 (13.0%) (Table 1). AKI incidence stratified by institution is presented in Supplementary Figure S2C. Univariate risk factors of AKI are presented in Supplementary Table S3. Factors associated with increased odds of developing AKI included older age; longer case duration; hypertension, diabetes, CHF, COPD, and CKD; norepinephrine equivalents >0.004 μg kg^{-1} min^{-1}, albumin use, and increased blood loss (Supplementary Figs S4 and S8A). Factors associated with decreased odds of developing AKI included being female, ASA class 1 and 2, cases using insufflation, pancreatectomies, use of nephrotoxic medications, and crystalloid administration >10 ml kg^{-1} h^{-1}.

Association between use of fluids and postoperative acute kidney injury

Our predictive model showed that an increase of crystalloid use from 1 to 10 ml kg^{-1} h^{-1} was associated with decreased risk of AKI by 58% among all patients (Fig. 3a, Supplementary Fig. S7A). There was a U-shaped pattern in the correlation between crystalloid use and risk of AKI, where both the extremes of crystalloid administration were associated with an increased risk. In subgroup analyses, patients with hypertension showed a stronger association between AKI and volume of crystalloid administered, whereas patients with CKD and CHF had weaker association (Fig. 3b–g).

Association between use vasopressors and postoperative acute kidney injury

Our predictive model showed that an increase in vasopressor use from 0 to 0.04 μg kg^{-1} min^{-1} of norepinephrine equivalents increased the risk of AKI in all patients by 1.8-fold (Fig. 4a, Supplementary Fig. S7B). This dose-dependent association was more profound in ASA 1 and 2 patients, whereas patients with CKD were the least affected (Fig. 4b–g). Importantly, when considering only patients who required a continuous vasopressor infusion, the dose-dependent association with risk of AKI was attenuated for all groups (Supplementary Fig. S5).

We observed a higher incidence of postoperative AKI in patients treated who required any type of vasopressor infusion. In addition, patients receiving vasopressor infusions also tended to be of a higher ASA class (3 or greater); to have a history of diabetes, hypertension, CHF, CKD, liver disease, or COPD; and longer surgical case duration (Supplementary Table S4).

Association between fluids, vasopressors use, and secondary outcomes

Overall, the rate of secondary outcomes was low (Supplementary Table S1). The total proportion of patients with KDIGO stage 2 or higher was 1.9%, and 30-day mortality was 0.3%. There was no significant difference in neither AKI Stage 2 or 3 nor 30-day mortality throughout the years in all patients (Table 1). In univariate analysis, patients who received continuous vasopressor infusions were more likely to develop severe AKI and had an increase in 30-day mortality (Supplementary Table S4). In our multivariable analysis, neither increased crystalloid administration nor increased vasopressor administration was associated

Table 1 Five-year trend and univariate analysis of patient characteristics and outcomes. *P-values calculated using the analysis of variance (ANOVA) test (means [SD]) or Kruskal–Wallis test (medians [IQR]) for continuous variables and χ^2 test for categorical variables. SMD < 0.1 is generally considered insignificant. ACEi, angiotensin-converting enzyme inhibitor; AKI, acute kidney injury, ARB, angiotensin-receptor blocker; COPD, chronic obstructive pulmonary disease; IQR, inter-quartile range; SMD, standardised mean differences; SD, standard deviation.

	2015 (*n*=6314)	2016 (*n*=6667)	2017 (*n*=6958)	2018 (*n*=6387)	2019 (*n*=5924)	P-value*	Smd
Age, yr, mean (SD)	57.9 (14.1)	58.0 (14.2)	58.5 (13.9)	58.6 (14.5)	59.0 (14.4)	<0.001	0.039
Female sex, *n* (%)	3279 (51.9)	3408 (51.1)	3548 (51.0)	3360 (52.6)	3241 (54.7)	<0.001	0.036
BMI, kg m^{-2}, mean (SD)	30.348 (8.195)	30.381 (8.326)	30.348 (8.206)	30.345 (8.302)	30.168 (8.180)	0.628	0.01
Race, *n* (%)						<0.001	0.093
Unknown	535 (8.5)	444 (6.7)	410 (5.9)	388 (6.1)	337 (5.7)		
Hispanic, White	54 (0.9)	63 (0.9)	71 (1.0)	101 (1.6)	86 (1.5)		
Black, non-Hispanic	638 (10.1)	686 (10.3)	715 (10.3)	687 (10.8)	698 (11.8)		
White, non-Hispanic	4842 (76.7)	5223 (78.3)	5473 (78.7)	4927 (77.1)	4503 (76.0)		
Asian or Pacific Islander	193 (3.1)	200 (3.0)	232 (3.3)	218 (3.4)	246 (4.2)		
ASA physical status, *n* (%)						<0.001	0.075
1	104 (1.6)	93 (1.4)	104 (1.5)	67 (1.0)	54 (0.9)		
2	2460 (39.0)	2587 (38.8)	2439 (35.1)	2265 (35.5)	2031 (34.3)		
3	3546 (56.2)	3787 (56.8)	4211 (60.5)	3882 (60.8)	3675 (62.0)		
4	204 (3.2)	200 (3.0)	204 (2.9)	173 (2.7)	164 (2.8)		
History of diabetes mellitus, *n* (%)	952 (15.1)	1011 (15.2)	1155 (16.6)	1079 (16.9)	1021 (17.2)	0.001	0.033
History of heart failure, *n* (%)	165 (2.6)	213 (3.2)	240 (3.4)	252 (3.9)	260 (4.4)	<0.001	0.047
History of hypertension, *n* (%)	2855 (45.2)	3233 (48.5)	3537 (50.8)	3275 (51.3)	3024 (51.0)	<0.001	0.059
History of renal failure, *n* (%)	362 (5.7)	437 (6.6)	536 (7.7)	572 (9.0)	537 (9.1)	<0.001	0.069
History of liver disease, *n* (%)	391 (6.2)	432 (6.5)	478 (6.9)	501 (7.8)	431 (7.3)	0.002	0.032
History of COPD, *n* (%)	865 (13.7)	966 (14.5)	994 (14.3)	1032 (16.2)	957 (16.2)	<0.001	0.038
Number of home medications, mean (SD)	3.554 (4.265)	3.700 (4.327)	3.917 (4.691)	4.726 (5.268)	5.132 (5.488)	<0.001	0.171
Use of ACEi or ARB, *n* (%)	725 (11.5)	788 (11.8)	966 (13.9)	1021 (16.0)	1006 (17.0)	<0.001	0.087
Surgical case duration (min), mean (SD)	253 (107)	255 (108)	256 (107)	259 (110)	261 (112)	<0.001	0.038
Case involving colon surgery, *n* (%)	1363 (21.6)	1523 (22.8)	1530 (22.0)	1492 (23.4)	1380 (23.3)	0.057	0.023
Case involving insufflation, *n* (%)	3198 (50.6)	3502 (52.5)	3805 (54.7)	3367 (52.7)	2957 (49.9)	<0.001	0.047
Case involving pancreatectomy, *n* (%)	298 (4.7)	300 (4.5)	352 (5.1)	293 (4.6)	308 (5.2)	0.277	0.017
Use of phenylephrine infusion, *n* (%)	831 (13.2)	1044 (15.7)	1231 (17.7)	1347 (21.1)	1514 (25.6)	<0.001	0.155
Requiring any vasopressor infusion, *n* (%)	857 (13.6)	1071 (16.1)	1266 (18.2)	1404 (22.0)	1584 (26.7)	<0.001	0.163
No vasopressor requirement, *n* (%)	2989 (47.3)	3029 (45.4)	2869 (41.2)	2579 (40.4)	2266 (38.3)	<0.001	0.094
Total crystalloid kg h^{-1}, median [IQR]	6.12 [3.84, 8.81]	5.88 [3.87, 8.28]	5.50 [3.69, 7.75]	5.19 [3.35, 7.32]	5.13 [3.28, 7.23]	<0.001	0.128
Total albumin per kg h^{-1}, mean (SD)	0.331 (0.826)	0.351 (0.814)	0.361 (0.853)	0.362 (0.851)	0.376 (0.833)	0.08	0.025
Proportion of patients receiving albumin, *n* (%)	1017 (16.1)	1219 (18.3)	1321 (19.0)	1272 (19.9)	1191 (20.1)	<0.001	0.05
Number of patients receiving <10 ml kg^{-1} h^{-1} crystalloid, *n* (%)	5205 (82.4)	5738 (86.1)	6127 (88.1)	5766 (90.3)	5307 (89.6)	<0.001	0.114
Patients receiving <10 ml kg^{-1} h^{-1} crystalloid AND vasopressor infusion, *n* (%)	671 (10.6)	877 (13.2)	1104 (15.9)	1246 (19.5)	1403 (23.7)	<0.001	0.175
Patients receiving >10 ml kg^{-1} h^{-1} crystalloid AND vasopressor infusion, *n* (%)	186 (2.9)	194 (2.9)	162 (2.3)	158 (2.5)	181 (3.1)	0.039	0.024
Norepinephrine equivalents kg^{-1} min^{-1}, median [IQR]	0.00029 [0.00, 0.0019]	0.00037 [0.00, 0.0021]	0.00059 [0.00, 0.0025]	0.00066 [0.00, 0.0031]	0.00083 [0.00, 0.0043]	<0.001	0.078

Continued

Table 1 Continued

	2015 (n=6314)	2016 (n=6667)	2017 (n=6958)	2018 (n=6387)	2019 (n=5924)	P-value*	Smd
Proportion of case duration spent hypotensive (MAP <65), %, median (IQR)	1.06 [1.02, 1.11]	1.08 [1.03, 1.14]	1.08 [1.04, 1.14]	1.08 [1.03, 1.14]	1.08 [1.04, 1.14]	<0.001	0.035
Total duration (min) of hypotension (MAP <65), mean (SD)	24.4 (31.4)	25.5 (33.6)	24.034 (32.3)	23.4 (30.8)	22.5 (28.9)	<0.001	0.037
Estimated blood loss (ml), mean (SD)	287 (535)	281 (511)	2667 (499)	257 (463)	265 (980)	0.037	0.027
Any AKI, *n* (%)	853 (13.5)	760 (11.4)	814 (11.7)	792 (12.4)	772 (13.0)	0.001	0.034
AKI Stage 1, *n* (%)	726 (11.5)	638 (9.6)	691 (9.9)	671 (10.5)	659 (11.1)	0.001	0.033
AKI Stage 2, *n* (%)	94 (1.5)	93 (1.4)	98 (1.4)	90 (1.4)	81 (1.4)	0.985	0.004
AKI Stage 3, *n* (%)	33 (0.5)	29 (0.4)	25 (0.4)	31 (0.5)	32 (0.5)	0.551	0.013
Mortality within 30 days of procedure, *n* (%)	17 (0.3)	20 (0.3)	22 (0.3)	14 (0.2)	16 (0.3)	0.888	0.018

with an increased 30-day mortality (Supplementary Figs S6 and S8B).

Discussion

In this multicentre, retrospective study of patients undergoing elective major abdominal surgery over 5 yrs, intraoperative fluids decreased and vasopressor use increased to maintain, if not slightly improve, intraoperative MAP. These changes in practice were seen with an initial decrease in the incidence of postoperative AKI from 2015 to 2016, followed by an increase through 2019. Furthermore, we observed a decreased risk of AKI with increasing intraoperative crystalloid administration and an increased risk of AKI with increasing vasopressor administration.

Although it is known that intraoperative hypotension is associated with AKI,[24] management of hypotension with fluid or vasopressor administration to maintain renal perfusion is variable. Initial trials demonstrated improved patient outcomes in major abdominal surgery from relative fluid restriction, including shorter length of stay.[26] However, increased renal complications with restrictive fluid administration occurred in the Restrictive versus Liberal Fluid Therapy for Major Abdominal Surgery (RELIEF) trial and a meta-analysis of 18 trials comparing liberal *vs* restrictive fluid approaches in major abdominal surgery.[27,28] In our study, the risk of AKI increased with fluid administration below 10 ml kg^{-1} h^{-1}, which is similar to the median volume of fluid administered in liberal arm of the RELIEF trial (10.9 ml kg^{-1} h^{-1}). Importantly, a majority of patients in our study received less than 10 ml kg^{-1} h^{-1} of crystalloid, which is more consistent with studied restrictive fluid practices. One retrospective study of noncardiac surgeries also found that there was a U-shaped association in the administration of perioperative fluids and overall complications, with patients in both the lowest and highest quintiles of fluid administration having the highest odds of postoperative complications.[29] We found that the benefits of increasing crystalloid administration up to 10 ml kg^{-1} h^{-1} was most marked in ASA 1 and 2 patients, although the U-shaped association was seen in all subgroups, including patients with hypertension and CHF. Although remaining confounding factors certainly persist, our results suggest that the changes in practice with respect to decreased crystalloid administration may be a contributory factor to an observed increase in the incidence of AKI after 2016.

Although we observed a decrease in the total duration of hypotension throughout the years, patients who received less than 10 ml kg^{-1} h^{-1} of crystalloid more likely received a vasopressor infusion in 2019 *vs* 2015. The evidence on using vasopressors to maintain kidney perfusion remains unclear, as vasopressor requirement often coincides with many underlying factors associated with illness severity (i.e. medical history, surgical complexity). In one randomised trial, early administration of vasopressors to maintain systolic arterial pressure was associated with less organ failure after surgery, including kidney injury.[30] Another randomised trial found targeting higher blood pressure did not reduce the risk of composite outcome of postoperative major adverse cardiovascular events, although a trend towards lower risk of severe AKI was observed.[31] An analysis of patients undergoing spine surgery found no difference in the odds of developing AKI between patients who required prolonged vasopressor infusions to maintain normotension, compared with their matched controls.[32] Our study highlights a complex interaction between dose of

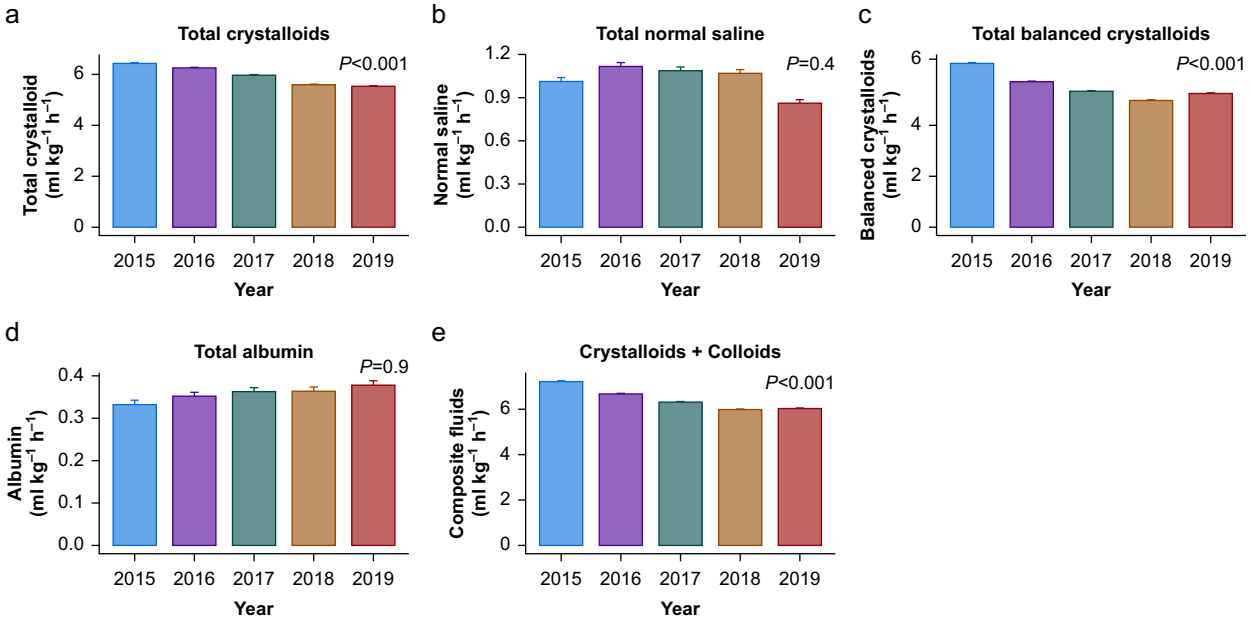

Fig 1. Five-year trend of fluid administration. Balanced crystalloids include Lactated Ringer's and Plasmalyte solutions. *P*-values for significant trend calculated using the Jonckheere–Terpstra test.

vasopressor, volume of fluids, and risk of AKI. An increase in use of norepinephrine equivalents from 0 to 0.04 μg kg^{-1} min^{-1} was associated with nearly a two-fold increased risk of AKI. We chose to use 0.04 μg kg^{-1} min^{-1} as the upper threshold, because it represents a clinically relevant dose of norepinephrine equivalents. However, because the majority of patients required no vasopressor at all, the confidence intervals increase at very low vasopressor doses, and the overall risk diminishes at higher doses. We believe that an association between vasopressor use and AKI may still exist for sicker patients. When we analysed only patients who required pressor infusions, the risk of AKI was attenuated most in healthy patients (ASA class 1 and 2), compared with sicker or older patients. Although no causality can be concluded from these observations, our data call into

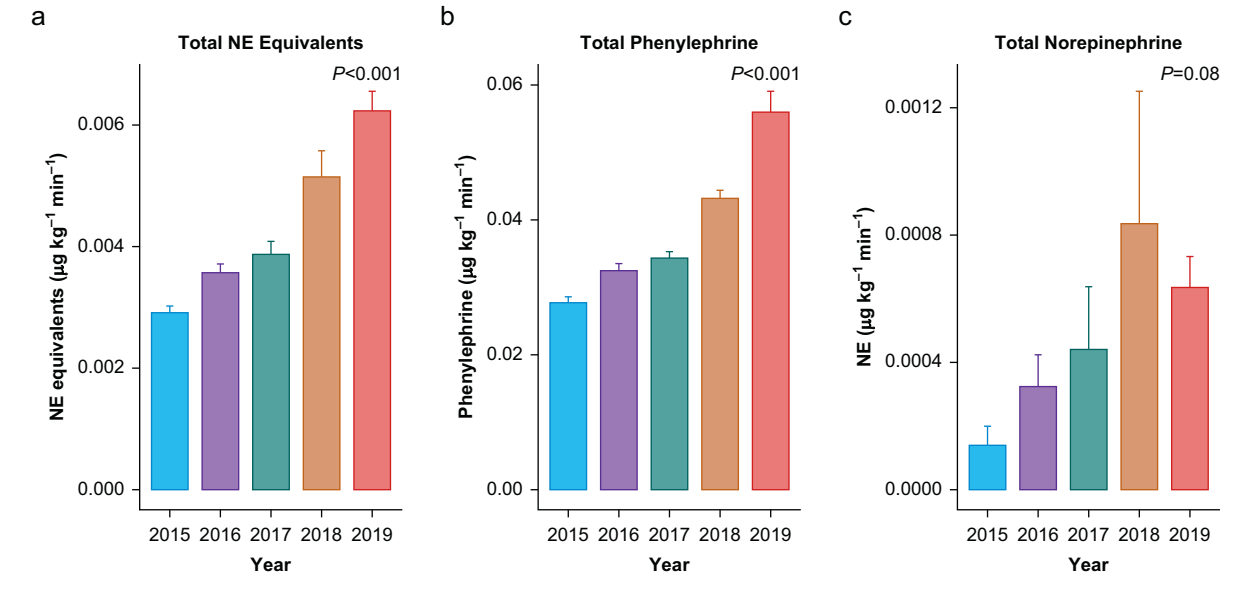

Fig 2. Five-year trend of vasopressor administration. *P*-values for significant trend calculated using the Jonckheere–Terpstra test. NE, norepinephrine.

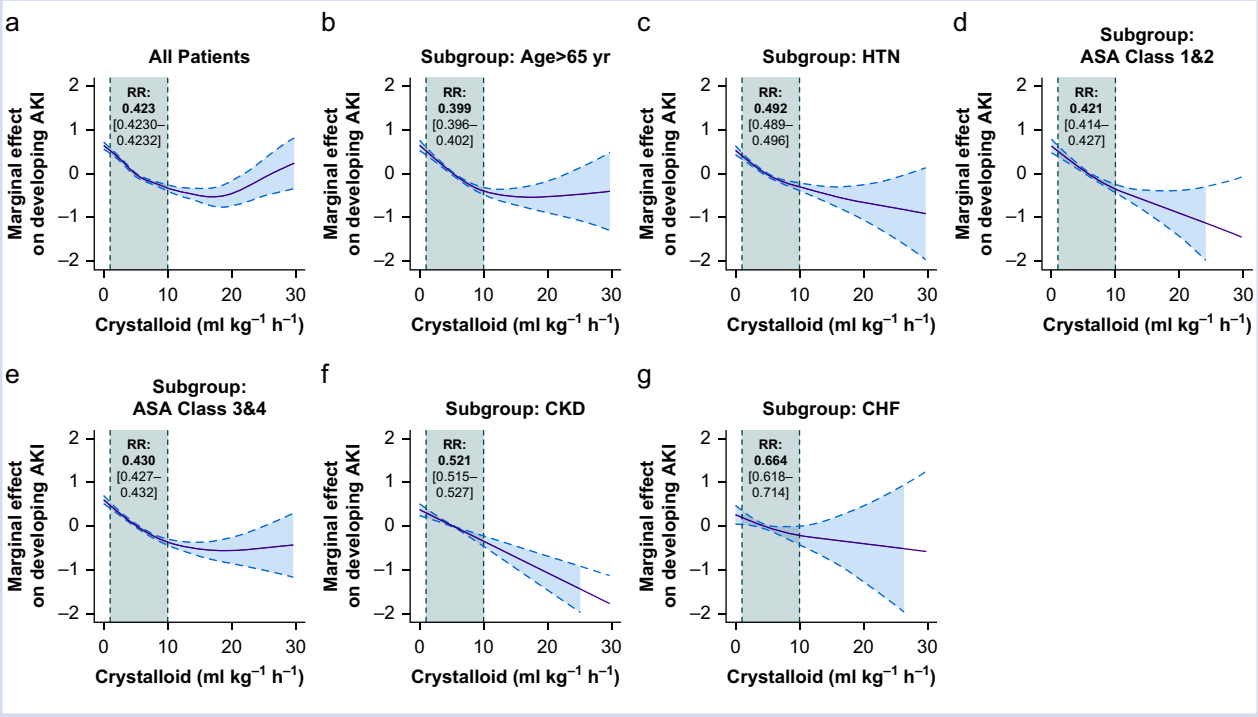

Fig 3. Partial dependence plots from generalised additive models to describe the relationship between risk of acute kidney injury and crystalloid administration among all patients (a) and multiple subgroups (b–g). Blue solid line represents the marginal impact of crystalloid administration on the development of acute kidney injury (AKI). Positive values indicate positive impact, negative values indicate negative impact. Black dotted lines represent 95% confidence intervals. Risk ratios (RRs) of developing AKI are calculated for an increase of 1–10 ml kg^{-1} h^{-1} in crystalloid administration (red dotted lines). CHF, congestive heart failure; CKD, chronic kidney disease; HTN, hypertension.

question a potential negative impact of strict blood pressure control with more liberal use of vasopressors. Notably, the concept that vasopressors can increase venous return and mimic an intrinsic fluid bolus through venous vasoconstriction may have contributed to restriction of fluids over the recent years.

Strengths of this large, multicentre, observational study include exploration of all aspects of haemodynamic management in patients undergoing major abdominal surgery that previous randomised trials with strict inclusion and exclusion criteria could not describe. For instance, the Intraoperative Norepinephrine to Control Arterial Pressure (INPRESS) trial explored the impact of tightly controlled systolic arterial pressure using pre-emptive norepinephrine, a restrictive fluid approach (lactated Ringer's infusion at 4 ml kg^{-1} h^{-1}), and boluses of 6% hydroxyethyl starch (administered in 250 ml boluses to achieve and maintain optimal stroke volume), whereas the RELIEF trial did not protocolise blood pressure targets or the use of vasopressors.[27,30] Although both high-quality trials have obviously impacted clinical practice, these trials only address the efficacy rather than the effectiveness of haemodynamic management within the general surgical population.

This study's retrospective design limits any causal inference made between practice pattern changes and postoperative outcomes. First, there were significant baseline changes over time in the patient population (including increasing age, ASA class, and number of comorbidities), and surgical complexity (including increasing case duration and intraoperative blood loss). When controlling for these baseline changes with multivariable regression, increased crystalloid administration was associated with a decreased risk of AKI, whereas increased vasopressor use was associated with an increased risk of AKI. It is important to note that certain factors are surrogates for illness severity. For instance, we found that cases involving insufflation were protective against AKI and 30-day mortality, which likely represents decreased surgical complexity. Similarly, use of nephrotoxic medications may reflect patients deemed to have lower risk of AKI and therefore more likely to receive such medications. Conversely, albumin may be chosen for more medically and surgically complex patients. Inter-institutional discrepancies and variability in reporting, and imperfect extraction of clinical concepts from the MPOG database, limit the overall generalisability of these analyses. We attempted to mitigate these discrepancies by removing extreme outlier values and avoiding imputation of missing variables. In studies using MPOG data, the incidence of AKI may be overestimated or underestimated because the definition of AKI was based on creatinine values alone, by removal of patients with missing data.[24] At the time of writing, the KDIGO definition of AKI remains widely accepted.[33] Biomarkers of subclinical AKI were not available for this cohort. Finally, it is unknown if patients received treatments based on perioperative goal-directed fluid therapy (GDFT) strategies or were enrolled in Enhanced Recovery After Surgery (ERAS) pathways, as such guidelines could have influenced practices on both an individual and institutional basis.

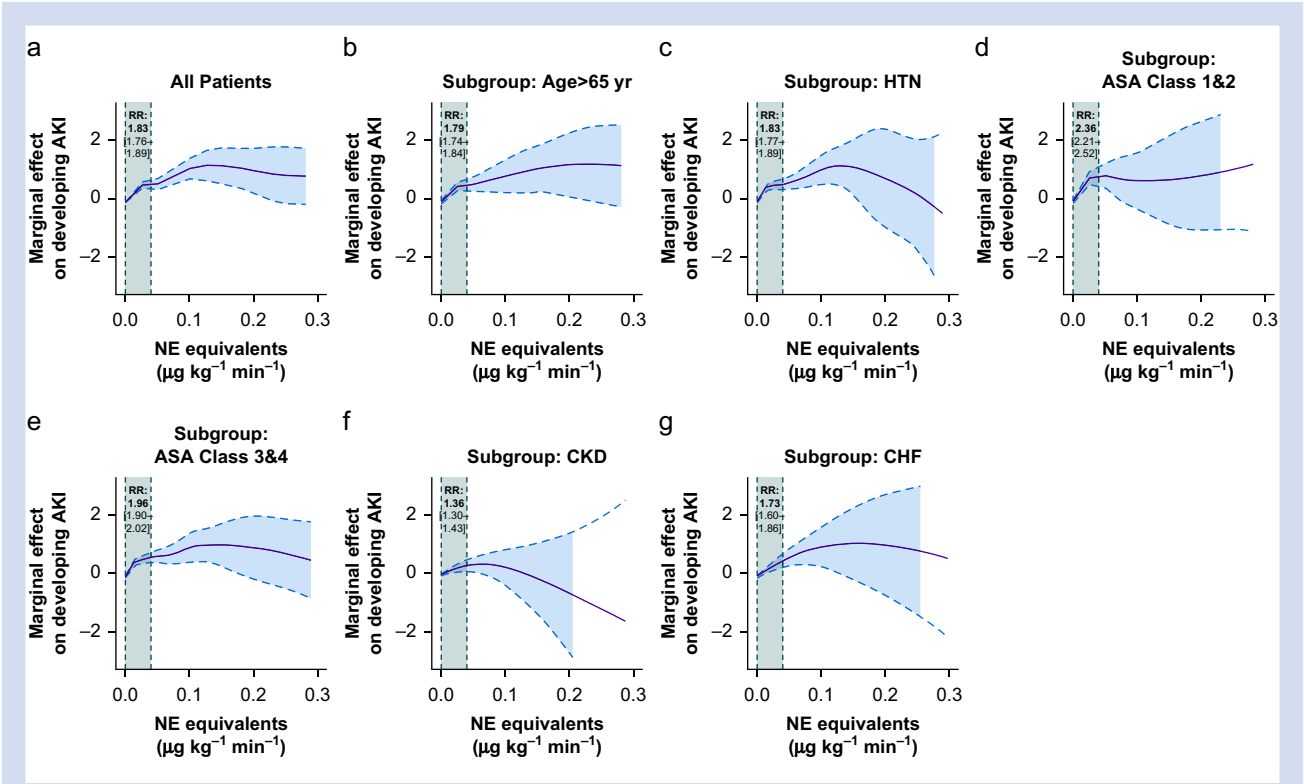

Fig 4. Partial dependence plots from generalised additive models to describe the relationship between risk of acute kidney injury and vasopressor administration among all patients (a) and multiple subgroups (b–g). Blue solid line represents the marginal impact of crystalloid administration on the development of acute kidney injury (AKI). Positive values indicate positive impact, negative values indicate negative impact. Black dotted lines represent 95% confidence intervals. Risk ratios (RRs) of developing AKI are calculated for an increase of 0–0.04 μg kg^{-1} min^{-1} in administration of norepinephrine equivalents (red dotted lines). CHF, congestive heart failure; CKD, chronic kidney disease; HTN, hypertension.

In summary, we observed changes in practice trends at 26 institutions between 2015 and 2019 with decreased intraoperative fluids and increased vasopressor use. During this study period, the duration of intraoperative hypotension decreased. We observed an association between crystalloid administration, vasopressor use, and the risk of acute kidney injury. Although no causality can be concluded, these data suggest that prevention and treatment of hypotension during abdominal surgery with liberal use of vasopressors at the expense of fluid administration is associated with an increased risk of postoperative acute kidney injury. Future investigations are warranted to assess the balance between fluids and vasopressor use with postoperative acute kidney injury.

Authors' contributions

Study design: CC, NF, DL, OM, LC, SK, KD, MM, ML
Data analysis: CC, NF, ML
Manuscript writing: CC, MM, ML
Manuscript review: NF, DL, OM, RK, LC, RP, SK, KD
Statistical analysis: RK, RP
Initial proposal review: SK, KD, MM

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Declarations of interest

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Perioperative Outcomes Group work collaboratively, the opinions, beliefs and viewpoints expressed by the authors do not necessarily reflect the opinions, beliefs, and viewpoints of Blue Cross Blue Shield of Michigan/Blue Care Network or any of its employees.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.05.002.

References

1. Tambyraja AL, Sengupta F, MacGregor AB, Bartolo DC, Fearon KC. Patterns and clinical outcomes associated with routine intravenous sodium and fluid administration after colorectal resection. *World J Surg* 2004; **28**: 1046–51. discussion 1051–2
2. Gustafsson UO, Scott MJ, Schwenk W, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery after Surgery (ERAS®) Society recommendations. *Clin Nutr* 2012; **31**: 783–800
3. Feldheiser A, Aziz O, Baldini G, et al. Enhanced Recovery after Surgery (ERAS) for gastrointestinal surgery: Part 2. Consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand* 2016; **60**: 289–334
4. Hobson C, Ruchi R, Bihorac A. Perioperative acute kidney injury: risk factors and predictive strategies. *Crit Care Clin* 2017; **33**: 379–96
5. Gumbert SD, Kork F, Jackson ML, et al. Perioperative acute kidney injury. *Anesthesiology* 2020; **132**: 180–204
6. Smith BB, Mauermann WJ, Yalamuri SM, et al. Intraoperative fluid balance and perioperative outcomes after aortic valve surgery. *Ann Thorac Surg* 2020; **110**: 1286–93
7. Kim M, Li G, Mohan S, Turnbull ZA, Kiran RP. Intraoperative data enhance the detection of high-risk acute kidney injury patients when added to a baseline prediction model. *Anesth Analg* 2021; **132**: 430–41
8. Porhomayon J, Davari-Farid S, Li CM, Arora P, Pourafkari L, Nader ND. Intraoperative administration of vasopressin during coronary artery bypass surgery is associated with acute postoperative kidney injury. *J Crit Care* 2015; **30**: 963–8
9. Furrer MA, Schneider MP, Löffel LM, Burkhard FC, Wuethrich PY. Impact of intra-operative fluid and noradrenaline administration on early postoperative renal function after cystectomy and urinary diversion: a retrospective observational cohort study. *Eur J Anaesthesiol* 2018; **35**: 641–9
10. MPOG. Perioperative Clinical research committee (PCRC) review. Available from: mpog.org/general-pcrc-information.
11. MPOG. Phenotype: Medical school affiliation. Available from: phenotypes.mpog.org/Medical%20School%20Affiliation.
12. Colquhoun DA, Shanks AM, Kapeles SR, et al. Considerations for integration of perioperative electronic health records across institutions for research and quality improvement: the approach taken by the Multicenter Perioperative Outcomes Group. *Anesth Analg* 2020; **130**: 1133–46
13. Sun E, Mello MM, Rishel CA, et al. Association of overlapping surgery with perioperative outcomes. *JAMA* 2019; **321**: 762–72
14. Kheterpal S, Vaughn MT, Dubovoy TZ, et al. Sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER): a multicenter matched cohort analysis. *Anesthesiology* 2020; **132**: 1371–81
15. Mavrothalassitis O, Pirracchio R, Fong N, et al. Outcome of surgical patients during the first wave of the COVID-19 pandemic in US hospitals. *Br J Anaesth* 2022; **128**: e35–7
16. Pirracchio R, Mavrothalassitis O, Mathis M, Kheterpal S, Legrand M. Response of US hospitals to elective surgical cases in the COVID-19 pandemic. *Br J Anaesth* 2021; **126**: e46–8
17. *Python 3 reference manual*. CreateSpace; 2009
18. MPOG. Phenotype: Total crystalloid administered, raw (ml). Available from: phenotypes.mpog.org/Total%20Crystalloid%20Administered,%20Raw%20(ml). (Accessed 25 January 2022)
19. Goradia S, Sardaneh AA, Narayan SW, Penm J, Patanwala AE. Vasopressor dose equivalence: a scoping review and suggested formula. *J Crit Care* 2021; **61**: 233–40
20. Walker H, Bell S. Strategies to reduce perioperative nephrotoxicity. *Semin Nephrol* 2019; **39**: 442–53
21. Davenport MS, Perazella MA, Yee J, et al. Use of intravenous iodinated contrast media in patients with kidney disease: consensus statements from the American College of Radiology and the National Kidney Foundation. *Radiology* 2020; **294**: 660–8
22. *R: a language and environment for statistical computing* 2021. Available from: http://www.R-project.org. (Accessed 19 November 2021)
23. Jonckheere A. A distribution-free k-sample test against ordered alternatives. *Biometrika* 1954; **41**: 133–45
24. Mathis MR, Naik BI, Freundlich RE, et al. Preoperative risk and the association between hypotension and postoperative acute kidney injury. *Anesthesiology* 2020; **132**: 461–75
25. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159**: 702–6
26. Aga Z, Machina M, McCluskey SA. Greater intravenous fluid volumes are associated with prolonged recovery after colorectal surgery: a retrospective cohort study. *Br J Anaesth* 2016; **116**: 804–10
27. Myles PS, Bellomo R. Restrictive or liberal fluid therapy for major abdominal surgery. *N Engl J Med* 2018; **379**: 1283
28. Messina A, Robba C, Calabrò L, et al. Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and metanalysis on randomised-controlled trials in major abdominal elective surgery. *Crit Care* 2021; **25**: 205
29. Miller TE, Mythen M, Shaw AD, et al. Association between perioperative fluid management and patient outcomes: a multicentre retrospective study. *Br J Anaesth* 2021; **126**: 720–9
30. Futier E, Lefrant JY, Guinot PG, et al. Effect of individualized vs standard blood pressure management strategies on postoperative organ dysfunction among high-risk patients undergoing major surgery: a randomized clinical trial. *JAMA* 2017; **318**: 1346–57
31. Wanner PM, Wulff DU, Djurdjevic M, Korte W, Schnider TW, Filipovic M. Targeting higher intraoperative blood pressures does not reduce adverse cardiovascular events following noncardiac surgery. *J Am Coll Cardiol* 2021; **78**: 1753–64

32. Farag E, Makarova N, Argalious M, et al. Vasopressor infusion during prone spine surgery and acute renal injury: a retrospective cohort analysis. *Anesth Analg* 2019; **129**: 896–904

33. Guthrie G, Guthrie B, Walker H, et al. Developing an AKI consensus definition for database research: findings from a scoping review and expert opinion using a Delphi process. *Am J Kidney Dis* 2022; **79**: 488–96. e1

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