

RESEARCH

Open Access



# Perioperative liberal versus restrictive fluid strategies and postoperative outcomes: a systematic review and meta-analysis on randomised-controlled trials in major abdominal elective surgery

Antonio Messina<sup>1,2\*</sup> , Chiara Robba<sup>3</sup>, Lorenzo Calabrò<sup>1</sup>, Daniel Zambelli<sup>1</sup>, Francesca Iannuzzi<sup>3,4</sup>, Edoardo Molinari<sup>3,4</sup>, Silvia Scarano<sup>3,4</sup>, Denise Battaglini<sup>3</sup>, Marta Baggiani<sup>5</sup>, Giacomo De Mattei<sup>6</sup>, Laura Saderi<sup>7</sup>, Giovanni Sotgiu<sup>7</sup>, Paolo Pelosi<sup>3,4</sup> and Maurizio Cecconi<sup>1,2</sup>

## Abstract

**Background:** Postoperative complications impact on early and long-term patients' outcome. Appropriate perioperative fluid management is pivotal in this context; however, the most effective perioperative fluid management is still unclear. The enhanced recovery after surgery pathways recommend a perioperative zero-balance, whereas recent findings suggest a more liberal approach could be beneficial. We conducted this trial to address the impact of restrictive vs. liberal fluid approaches on overall postoperative complications and mortality.

**Methods:** Systematic review and meta-analysis, including randomised controlled trials (RCTs). We performed a systematic literature search using MEDLINE (via Ovid), EMBASE (via Ovid) and the Cochrane Controlled Clinical trials register databases, published from 1 January 2000 to 31 December 2019. We included RCTs enrolling adult patients undergoing elective abdominal surgery and comparing the use of restrictive/liberal approaches enrolling at least 15 patients in each subgroup. Studies involving cardiac, non-elective surgery, paediatric or obstetric surgeries were excluded.

**Results:** After full-text examination, the meta-analysis finally included 18 studies and 5567 patients randomised to restrictive (2786 patients; 50.0%) or liberal approaches (2780 patients; 50.0%). We found no difference in the occurrence of severe postoperative complications between restrictive and liberal subgroups [risk difference (95% CI) = 0.009 (− 0.02; 0.04); *p* value = 0.62; *I*<sub>2</sub> (95% CI) = 38.6% (0–66.9%)]. This result was confirmed also in the subgroup of five studies having a low overall risk of bias. The liberal approach was associated with lower overall renal major events, as compared to the restrictive [risk difference (95% CI) = 0.06 (0.02–0.09); *p* value = 0.001]. We found no difference in either early (*p* value = 0.33) or late (*p* value = 0.22) postoperative mortality between restrictive and liberal subgroups

\*Correspondence: antonio.messina@humanitas.it

<sup>1</sup> Department of Anaesthesia and Intensive Care Medicine, Humanitas Clinical and Research Center – IRCCS, Via Alessandro Manzoni, 56, 20089 Rozzano, MI, Italy

Full list of author information is available at the end of the article



© The Author(s) 2021. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

**Conclusions:** In major abdominal elective surgery perioperative, the choice between liberal or restrictive approach did not affect overall major postoperative complications or mortality. In a subgroup analysis, a liberal as compared to a restrictive perioperative fluid policy was associated with lower overall complication renal major events, as compared to the restrictive.

**Trial Registration:** CRD42020218059; Registration: February 2020, [https://www.crd.york.ac.uk/prospero/display\\_record.php?RecordID=218059](https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=218059).

**Keywords:** Liberal, Restrictive, Fluid therapy, Postoperative complications, Postoperative mortality

## Introduction

A worldwide effort aims to reduce postoperative complications [1], which are recognised as partially preventable events affecting long-term morbidity and impacting health and financial systems [2, 3]. Several perioperative strategies have been proposed to optimise intraoperative management and postoperative care [4]. Among them, perioperative fluid therapy is a core concept. The ideal perioperative approach has been debated for decades, having the crucial role of balancing oxygen supply and demand, maintaining fluid and electrolyte homeostasis and avoiding inadequate tissue perfusion and fluid overload [5–12].

The most effective perioperative fluid management is still unclear [13–15]. It has been classified as restrictive (<1.75 L per day), balanced (1.75 to 2.75 L per day) and liberal (>2.75 L per day) [16]. However, the literature provides different, somewhat overlapping definitions (*i.e.* from 1.0 to 2.7 L for restrictive, compared with 2.8 to 5.4 L for liberal fluid regimens) [17] and conflicting evidence [13–15]. The enhanced recovery after surgery (ERAS) pathways to support early recovery among patients undergoing major surgery recommend a restrictive approach aiming at the perioperative “zero-balance” [13]. In contrast, recent findings suggest that excessively restrictive approaches could be detrimental, indicating that a moderately liberal fluid regimen (*i.e.* positive fluid balance of 1 to 2 L at the end of surgery) might be the best approach [14].

Interestingly, a recent large randomised controlled trial (RCT) assigning 2983 patients to either zero-balance or liberal strategy showed comparable disability-free survival outcome, although the zero-balance approach was associated with a higher rate of acute kidney injury [16]. As a matter of fact, this single study enrolled more patients than several previous RCTs regarding this topic, insofar, partially challenging previous results [18–20].

Therefore, we conducted an up-to-date meta-analysis of RCTs to assess the association between restrictive and liberal strategies and major adverse surgical outcomes in elective surgery.

Secondarily, we appraised the association between restrictive and liberal approaches on perioperative

mortality, predefined postoperative organ-related complications and hospital length of stay. Finally, we stratified the studies according to preoperative severity score and the reported rate of complications [*i.e.* American Society of Anaesthesiologists (ASA) physical status score].

## Materials and methods

We adhered to the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis—Protocols* (PRISMA-P) guidelines [21] (Additional file 1: Table 1) and the study protocol was registered [*International Prospective Register of Systematic Reviews—PROSPERO* (CRD42020218059)].

### Data sources and search strategy

A systematic literature search was performed by using the following databases to identify relevant studies in indexed scientific journals: MEDLINE (via Ovid), EMBASE (via Ovid) and the Cochrane Controlled Clinical trials register, by using the terms: [(“liberal” OR “restrictive” OR “zero-balance” AND (“surgery”/exp OR surgery))] with filters for humans, age (<18 years), language (English) and time of publication (1 January 2000 to 31 December 2019).

We included RCTs 1) enrolling adult patients undergoing elective abdominal surgery; 2) comparing two different regimes of fluid administration defined as “restrictive” and “liberal” or “conventional” or “standard”; 3) starting the study protocol intraoperatively; 4) reporting postoperative complications or mortality or as primary or secondary outcomes.

The restrictive approach was defined as a modality of perioperative (*i.e.* intraoperative and during the first 24 h after surgery) treatment employing a specific and predefined treatment protocol to obtain in one of the enrolled populations an overall negative or zero fluid balance, as compared to the other. Accordingly, trials showing no statistically significant difference in the overall fluid intake or balance, between restrictive and liberal subgroups, were also excluded.

Studies involving cardiac, non-elective surgery, paediatric or obstetric surgeries were excluded. We also excluded editorials, commentaries, letters to the editor,

opinion articles, reviews, meeting abstracts and original articles lacking abstract and/or quantitative details, or those enrolling less than 15 patients in each subgroup.

The references of all included papers, review articles, commentaries and editorials on this topic were also reviewed to identify other studies of interest missed during the primary search.

#### Data extraction and quality assessment

Three couples of examiners (S.S., E.M., D.B., F.I., M.B., G.D.M.) independently evaluated titles and abstracts. The articles were then subdivided into three subgroups: “included” and “excluded” (if the two examiners agreed with the selection) or “uncertain” (in case of disagreement). In the case of “uncertain” classification, discrepancies were resolved by further examination performed by two expert authors (A.M. and C.R.). We used a standardised electronic spreadsheet (Microsoft Excel, V 14.4.1; Microsoft, Redmond, WA) to extract the data from all included studies, recording trial characteristics (the complete data reporting sheet is provided in Additional file 1: Table 2). When necessary, the included studies’ corresponding authors were contacted to obtain missing data related to trial demographics, methods and outcomes.

#### Risk of bias assessment in the included studies

Two examiners (L.C. and D.Z.) independently assessed the internal validity of the included studies and discrepancies were resolved by a third senior author (A.M. or C.R.), by using the RoB 2 (a revised Cochrane Collaboration’s risk of bias tool for randomised trials) [22]. The RoB 2 considers five bias domains: 1) the randomisation process; 2) the deviations from intended interventions; 3) missing outcome data; 4) measurement of the outcome; 5) selection of the reported results. Finally, the overall risk of bias was calculated and, accordingly, studies were included in either high-risk/ some concerns /low-risk groups.

#### The strength of the body of evidence

The strength of the body of evidence was assessed according to the *Grading of Recommendations, Assessment, Development and Evaluations* (GRADE) evidence system [23].

#### Outcomes definitions

Our primary outcome was to appraise the effect of restrictive vs liberal approaches on the overall rate of major complications. This outcome was assessed both considering all the studies reporting it, and those in the subgroup having a low-risk of bias, according to the RoB 2 scale.

Secondary outcomes were: to evaluate the association between restrictive and liberal approaches on perioperative early ( $\leq 30$  postoperative days) and late (i.e.  $> 30$  postoperative days) mortality and predefined postoperative major complications: renal (i.e. worsening of renal function, according to the trial definition); cardiovascular [i.e. pulmonary not infective complications, cardiac ischemic dysfunction/failure, cardiac arrhythmias; acute neurological events]; infections (i.e. all infective complications reported, including the occurrence of either sepsis or septic shock). We also evaluated the length of hospital stay and stratified the studies according to the enrolled patients’ ASA classification.

#### Statistical analysis

Statistical analysis was conducted on the summary statistics described in the selected articles (e.g. means, medians, proportions) and, therefore, the statistical unit of observation for all the selected variables was the single study and not the patient. Descriptive statistics of individual studies used different statistical indicators for central tendency and variability, such as means and standard deviations, whereas absolute and relative frequencies were adopted for qualitative variables. To show one single indicator for the quantitative variables we collected means with standard deviations (SD) or medians and inter-quartile ranges (IQR) were used, as appropriate.

The metaanalysis included only those studies reporting mortality and rate of complications, according to the definition adopted in each study and expressed as rate with respect of the enrolled populations. For ASA subgroup analysis, we grouped studies with at least 50% of the included population classified as ASA I/II, compared to those having at least 50% of the included population classified as ASA III/IV. We, finally, stratified the studies according to three tertiles of the overall amount of perioperative fluid given (day 0 and day 1) and the rate of major events.

We assessed publication bias using a funnel plot for the considered outcomes. Statistical heterogeneity and inconsistency were measured using  $Q$  and  $I^2$  tests and were deemed to be significant when  $p < 0.1$  and  $I^2 > 50\%$ . According to heterogeneity, random or fixed-effect models were used to perform metaanalysis. According to Higgins et al. [24],  $I^2$  values around 25, 50 and 75% were considered representing, respectively, low, moderate and severe statistical inconsistency.

The statistical software STATA<sup>®</sup>13 (StataCorp, College Station, TX, USA) was used to perform all the computations.

## Results

We identified 26 potentially eligible studies after the title and abstract assessment (Fig. 1 and Additional file 1: Table 3). After full-text examination, the meta-analysis finally included 18 studies and 5567 patients (male/female ratio 1.1:1) randomised to restrictive (2786 patients; 50.0%) and liberal approaches (2780 patients; 50.0%). All the studies, except one [25], have been conducted on non-obese patients, the vast majority being scheduled for laparotomic (3925 patients, 70.5%) surgery. All the studies, except two [25, 26], were conducted on patients with a median age > 60 years old (Table 1). Interestingly, in 5 studies (27.7%), including the largest one [16], the perioperative fluid administration algorithm was guided by the optimisation of predefined or flow haemodynamic pressure variables, by means of a goal-directed therapy [16, 25, 27–29] (Additional file 1: Table 4).

The risk of bias assessment reported: “low risk” for 8 (44.4%) and “some concerns” for 11 (55.5%) of the included studies, mostly (9 of these 11; 81.8%) related to the selection of the reported results (Fig. 2).

Following the GRADE system, the quality of evidence was defined as high for 8 studies [16, 25, 30–35] and moderate for all the others.

### Perioperative fluid administration, balance and weight gain

Intraoperatively, patients in the restrictive subgroup overall received a median (IQR) of 1925 (1482–2470) of fluids, as compared to 3878 (3000–4400) of the liberal subgroup. On day 0 (*i.e.* considering the overall amount of fluids received on the day of the operation, including intraoperative fluid therapy), patients in the restrictive subgroup overall received a median (IQR) of 2341 ml (1635–3530) of fluids, as compared to 4,350 ml (3095–5326) in the liberal subgroup. Finally, considering day 0 and day 1, a median of 3617 (2897–5291) of fluids was administered to the restrictive subgroups, as compared to 5820 (5038–7000) to the liberal subgroups (Table 2 and Additional file 1: Table 4).

Only two studies reported the mean postoperative overall fluid balance among restrictive and liberal subgroups [16, 33]. Nine studies (50.0%) did not report postoperative weight gain [25, 26, 29–31, 33, 34, 36, 37], moreover, in Myles et al.'s study, data regarding this variable were missing for 1,036 (69.5%) patients in the restrictive fluid group and 999 (66.9%) in the liberal fluid group [16].

Five studies (27.7%) [16, 28, 35, 38, 39] reported a median (IQR) weight gain of 0.3 kg (– 0.1 to 0.65) and 2.0 kg (1.7–2.6) in restrictive and liberal groups on postoperative day 1, respectively.

### Primary outcome: rate of major complications

Pooling data from the 13 studies, we found no difference in the occurrence of major postoperative complications between restrictive and liberal subgroups [pooled risk difference (95% CI) = 0.009 (– 0.02; 0.04);  $\text{Chi}_2 = 0.24$ ;  $p$  value = 0.62;  $I_2$  (95% CI) = 38.6% (0–66.9%)] (Fig. 3). In the subgroup of five studies [16, 25, 30–32] reporting the outcome of major postoperative events and having a low overall risk of bias, we found no difference between restrictive and liberal subgroups [pooled risk difference (95% CI) = 0.013 (– 0.02; 0.05);  $\text{Chi}_2 = 0.42$ ;  $p$  value = 0.51;  $I_2$  (95% CI) = 1.0% (0–64.5%)].

### Secondary outcomes

#### Postoperative mortality

We found no difference in either early [data pooled from the 10 studies—pooled risk difference = – 0.005 (95% CI – 0.016 to 0.005);  $\text{Chi}_2 = 0.95$ ;  $p$  value = 0.33;  $I_2 = 0\%$  (95% CI 0% to 52.7%)] or late [data pooled from the 8 studies—pooled risk difference = 0.005 (95% CI – 0.003 to 0.012);  $\text{Chi}_2 = 1.51$ ;  $p$  value = 0.22;  $I_2$  (inconsistency) = 0% (95% CI 0–56.3%)] postoperative mortality between restrictive and liberal subgroups (Additional file 1: Figures 1–2).

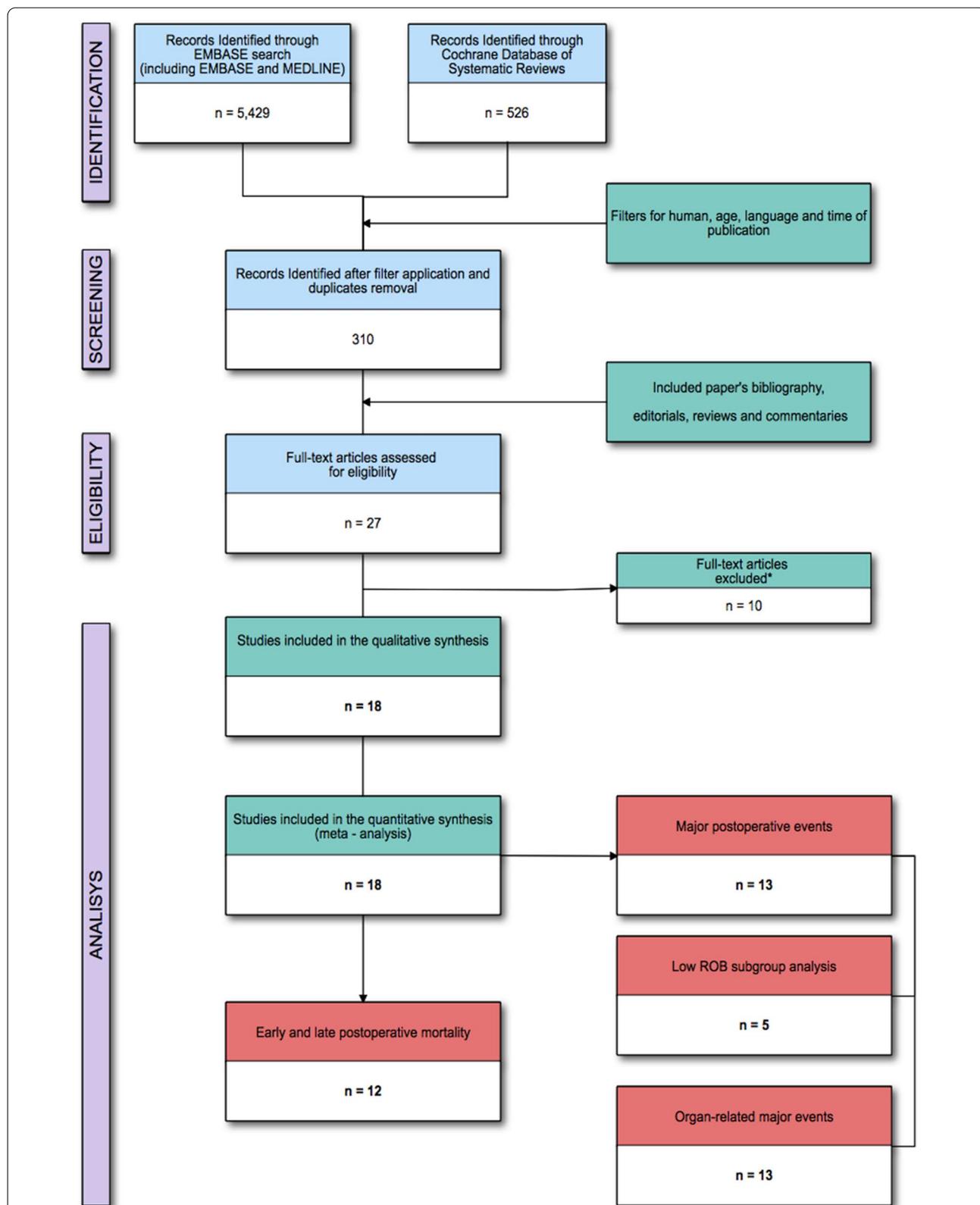
#### Postoperative organ-related major complications and length of stay

Pooling data from the 8 studies, the liberal approach was associated with lower overall complication renal major events, as compared to the restrictive [pooled risk difference (95% CI) = 0.06 (0.02–0.09);  $\text{Chi}_2 = 10.3$ ;  $p$  value = 0.001] (Fig. 4). In this subgroup, a sub-analysis regarding the use of type of fluid used intraoperatively (colloids vs. crystalloids) showed a borderline statistical significance regarding an increased incidence of major renal events in the restrictive populations receiving colloids, as compared to the liberal ones [mean (SD) major renal events 8.0% (4.7) vs. 1.7% (1.9);  $p = 0.05$ ].

On the contrary, we found no difference between restrictive and liberal subgroups in the occurrence of either severe postoperative cardiovascular (9 studies;  $p$  value = 0.88) or infective (10 studies;  $p$  value = 0.10) complications (Additional file 1: Figures 3–4), or the length of hospital stay [7 days (6–9) vs. 7 days (5–8);  $p$  value = 0.49].

#### Subgroup analyses

As reported in Additional file 1: Table 5, preoperative ASA risk score did not impact the postoperative complications rate, among restrictive/liberal subgroups. No difference in the overall rate of major complications was found by stratifying the in tertiles of overall perioperative fluid administered (Fig. 5).



**Fig. 1** Flow of the studies. \* = Not fitting eligibility criteria full-text articles excluded are reported in Additional file 1: Table 3. ROB, risk of bias

**Table 1** Summary of the included studies: general characteristics of the enrolled population

References	Year	Pt. analysed n (%)	RES n (%)	LIB n (%)	Age (years)	BMI (kg/m <sup>2</sup> )		ASA I, n (%)		ASA II, n (%)		ASA III-IV, n (%)	
						RES	LIB	RES	LIB	RES	LIB	RES	LIB
Brandstrup [46]	2003	141	69 (48.9)	72 (51.1)	64	69	25	34 (49.3)	32 (44.4)	33 (47.8)	39 (54.2)	2 (2.9)	1 (1.4)
Kabon [26]	2005	253	124 (49)	129 (51)	53	52	NA	13 (10.5)	9 (7.0)	81 (65.3)	86 (66.7)	30 (24.2)	34 (26.4)
Nisanevich [28]	2005	152	77 (50.7)	75 (49.3)	63	59	25	15 (19.5)	19 (25.3)	42 (54.5)	37 (49.3)	20 (26)	19 (25.3)
Holte [39]	2007	32	16 (50)	16 (50)	74	77	24	5 (31.2)	3 (18.8)	2 (12.5)	5 (31.2)	8 (50)	9 (56.2)
Muller [37]	2009	151	76 (50.3)	75 (49.7)	62	59	24	2 (2.6)	3 (4.0)	50 (65.8)	54 (72)	24 (31.6)	18 (24)
Futier [36]	2010	70	36 (51.4)	34 (48.6)	62	60	25	19 (52.8)	20 (58.8)	9 (25)	6 (17.6)	8 (22.2)	7 (20.6)
Gao [30]	2012	179	93 (52)	86 (48)	72	73	22	33 (35.5)	32 (37.2)	27 (29)	24 (27.9)	33 (35.5)	30 (34.9)
Matot [25]	2012	107	52 (48.6)	55 (51.4)	40	42	44	0 (0.0)	0 (0.0)	33 (63.5)	38 (69.1)	19 (36.5)	17 (30.9)
Abraham [38]	2012	161	82 (50.9)	79 (49.1)	68	69	25	19 (23.1)	21 (26.6)	49 (59.7)	53 (67.1)	11 (14.4)	8 (10.1)
Kalyan [32]	2013	239	121 (50.6)	118 (49.4)	70	70	26	28 (23.1)	17 (14.4)	70 (57.9)	75 (63.6)	23 (19.0)	26 (22.0)
Lavu [33]	2014	250	131 (52.4)	128 (51.2)	67	68	27	NA	NA	NA	NA	83 (63.4)	84 (65.6)
Hong-Ying [49]	2014	185	89 (48.1)	96 (51.9)	65	65	22	29 (32.6)	30 (31.3)	37 (41.6)	41 (42.7)	23 (25.8)	25 (26)
Piljic [34]	2015	60	30 (50)	30 (50)	69	69	25	NA	NA	NA	NA	NA	NA
van Samkar [47]	2015	54	30 (55.6)	24 (44.4)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Grant [31]	2016	330	166 (50.3)	164 (49.7)	65	65	27	7 (4.2)	6 (3.7)	88 (53)	90 (54.9)	71 (42.8)	68 (41.5)
Kassim [29]	2016	50	25 (50)	25 (50)	67	66	NA	NA	NA	NA	NA	NA	NA
Myles [16]	2018	2983	1490 (49.9)	1493 (50.1)	66	66	NA	25 (1.7)	21 (1.4)	542 (36.4)	540 (36.2)	923 (61.9)	932 (62.4)
Wuethrich [35]	2014	166	83 (50.0)	83 (50.0)	69	68	24	0 (0.0)	0 (0.0)	52 (63)	46 (55)	31 (37)	37 (45)

N: number of patients; NA: data not available; ASA: American Society of Anaesthesiologists physical status; RES/LIB refers to those patients who received restrictive or liberal strategy, respectively. Age and body mass index (BMI) columns report the mean/median values of the LIB/RES populations recorded in each study

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Brandstrup et al 2003	+	+	+	+	?	!
Kabon et al 2005	+	+	+	+	?	!
Nisanevich et al 2005	+	+	+	+	?	!
Holte et al 2007	+	+	+	+	?	!
Muller et al. 2009	?	?	+	+	+	!
Futier et al 2010	+	+	+	+	?	!
Gao et al. 2012	+	+	+	+	+	+
Matot et al 2012	+	+	+	+	+	+
Abraham-nordling et al 2012	+	+	+	+	?	!
Kalyan et al 2013	+	+	+	+	+	+
Lavu et al 2014	+	+	+	+	+	+
Hong-ying et al 2014	+	+	+	+	?	!
Piljic et al 2015	+	+	+	+	+	+
Van Samkar et al 2015	+	+	+	+	?	!
Grant et al 2016	+	+	+	+	+	+
Kassim et al 2016	+	+	+	+	?	!
Myles et al 2018	+	+	+	+	+	+
Wuethrich et al. 2014	+	+	+	+	+	+

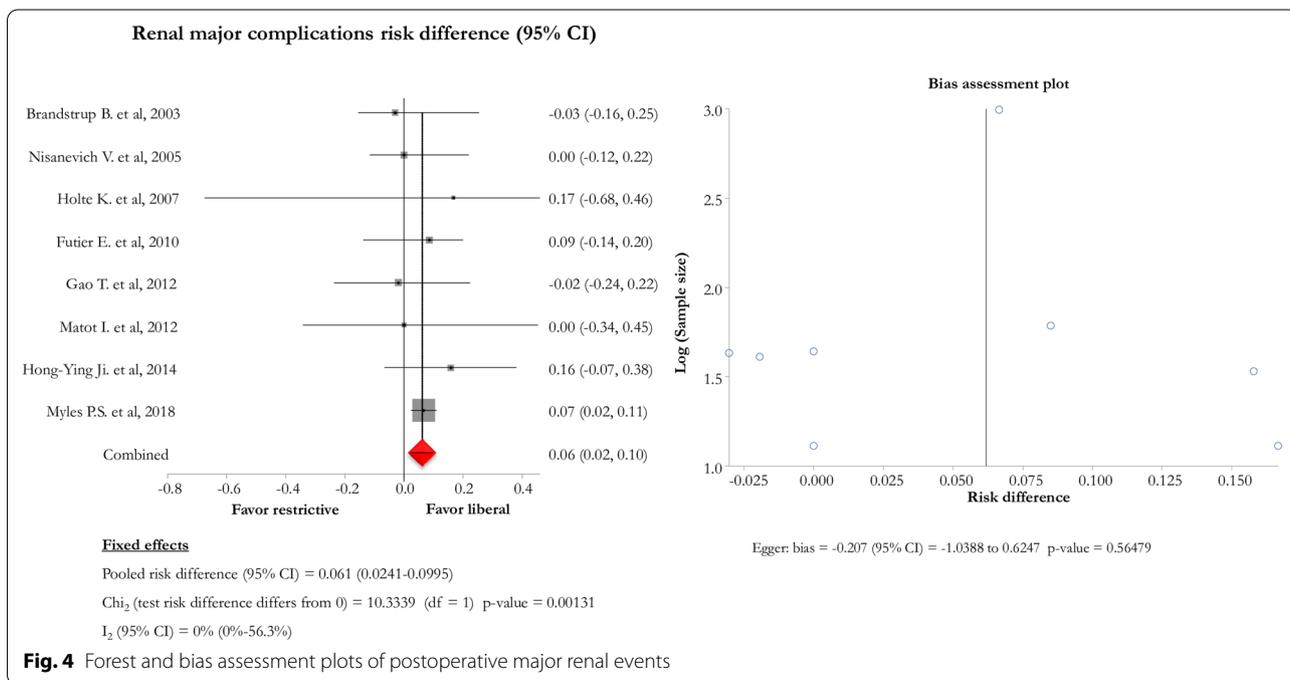
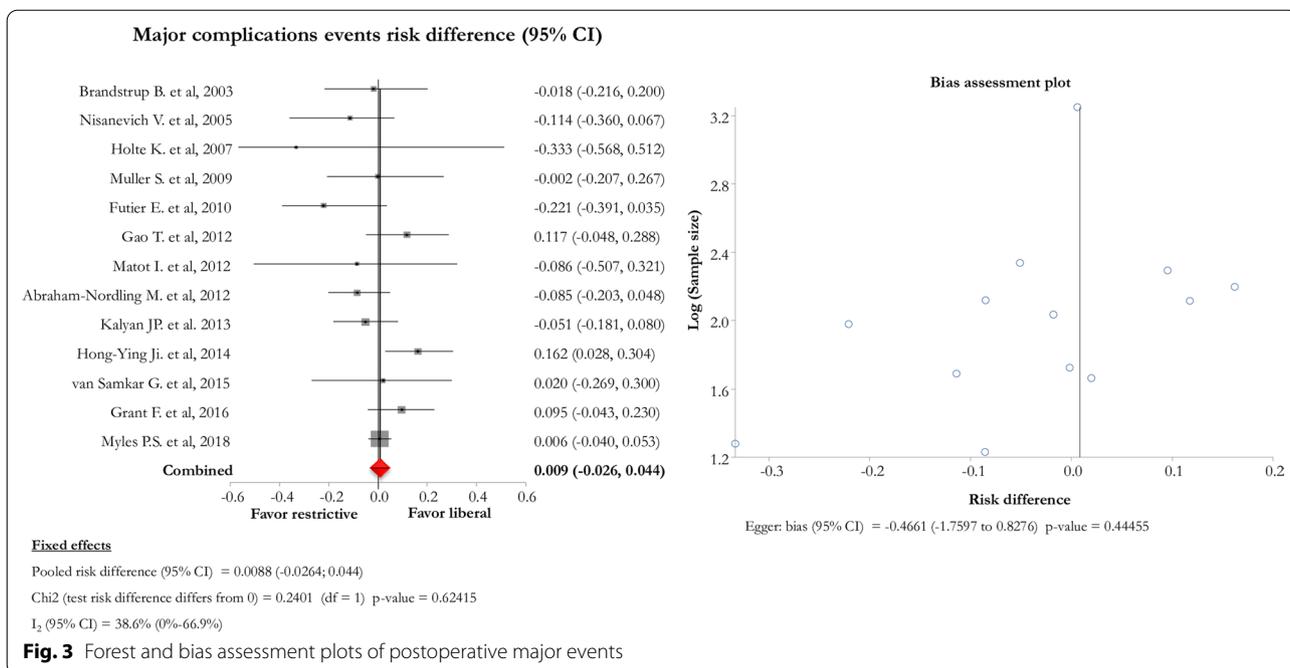
 Low risk  
 Some concerns  
 High risk

**Fig. 2** The internal validity of the included studies was assessed by two expert authors, by using the Rob2: a revised Cochrane Collaboration's risk of bias tool for randomised trials [22]

**Table 2** Summary of the included studies: fluid infused on day 0 and day 1

References	IO COLLOIDS (%)			COLLOIDS IO (ml)			CRYSTALLOIDS IO (ml)			TOTAL FLUIDS IO (ml)			FLUIDS DAY 0 (IO + PO) (ml)			FLUIDS DAY 1 (ml)		
	LIB	RES	LIB	LIB	RES	LIB	LIB	RES	LIB	RES	LIB	LIB	RES	LIB	RES	LIB	RES	
Brandstrup [46]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5388 (2700–11,083)	2740 (1100–8050)	1500 (0–6000) D1	500 (0–5000) D1			
Kabon [26]	0	0	0	3900 (1900)	2500 (1300)	NA	NA	NA	NA	NA	NA	5000 (400)	3100 (300)	NA	NA	NA	NA	
Nisanevich [28]	NA	NA	NA	NA	NA	NA	3878 (1170)	1408 (946)	NA	NA	NA	3878 (1170)	1408 (946)	2012 (475) D1	2170 (476) D1			
Holte [39]	11.3	30.4	500 (350–750)	500 (341–850)	3900 (2722–6500)	1140 (580–1500)	NA	NA	NA	NA	NA	5050 (3563–8050)	1640 (935–2250)	NA	NA	NA	NA	
Muller [37]	NA	NA	NA	NA	NA	NA	2950 (1600–6400)	1925 (1100–6700)	NA	NA	NA	2950 (1600–6400)	1925 (1100–6700)	2700 (1800–9100) D1	1200 (3900–9900) D1			
Futier [36]	5.6	25.2	316 (311)	854 (547)	5266 (1340)	3040 (769)	NA	NA	NA	NA	NA	5588 (1463)	3380 (1114)	NA	NA	NA	NA	
Gao [30]	40.6	13.5	1240 (410)	210 (300)	1450 (310)	1320 (220)	3050 (800)	1555 (410)	NA	NA	NA	3050 (800)	1555 (410)	2730 (560) D1	2100 (340) D1			
Matot [25]	NA	NA	NA	NA	NA	NA	3300 (1500–14,000)	1325 (480–3100)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Abraham [38]	0	0	0 (0–500)	0 (0–200)	2500 (2000–3070)	575 (452–800)	NA	NA	NA	NA	NA	5775 (5050–6700)	3050 (2662–3328)	NA	NA	NA	NA	
Kalyan [32]	NA	NA	NA	NA	NA	NA	2033 (1576–2500)	1000 (690–1500)	NA	NA	NA	NA	NA	3315 (2645–3894) D1	1944 (1354–2515) D1			
Lavu [33]	0	0	0	0	6694	4812	6694	4812	NA	NA	NA	8789	5731	3312	3042			
Hong-Ying [49]	NA	NA	NA	NA	NA	NA	3110	1620	NA	NA	NA	NA	NA	2750 (570) D1	2090 (360) D1			
Piljic [34]	25.9	15.9	675 (513)	315 (409)	1923 (593)	1662 (655)	2598 (505)	1977 (528)	NA	NA	NA	5017	4038	2613 (549) D1	2006 (549) D1			
van Samkar [47]	22.7	40.0	1000 (0.6)	1400 (0.6)	3400 (2500–6000)	2100 (1600–2500)	NA	NA	NA	NA	NA	NA	NA	2500	2500			
Grant [31]	9.2	15.9	363 (0–4000)	390 (0–2500)	3563 (1050–7550)	2050 (650–5130)	NA	NA	NA	NA	NA	2151 (1030–4856)	1178 (550–4791)	2577 (1650–6500) D1	1436 (1000–4245) D1			
Kassim [29]	20.4	50.0	920 (206)	1219 (268)	3586 (473)	1219 (140)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Myles [16]	14.2	22.9	500 (400–1000)	500 (250–800)	3000 (2100–3850)	1677 (1173–2294)	NA	NA	NA	NA	NA	4300	2737	3100	2056			
Wuethrich [35]	0	0	0	0	4300 (2800–6200)	1700 (700–4000)	4300 (2800–6200)	1700 (700–4000)	NA	NA	NA	NA	NA	2050 (1000–4100)	2100 (800–4000)			

Data are reported with the appropriate ranges, according to those present in the included studies. Data without ranges are obtained from data reported in the study. LIB, liberal; RES, restrictive; IO, intraoperative; PO, postoperative (including the whole period after the operation spent either in recovery room or intensive care unit); DAY 1, first day after the operation; NA, data not available. The first column reports the overall rate of intraoperative rate of colloids administration, as compared to the overall intraoperative amount of fluids

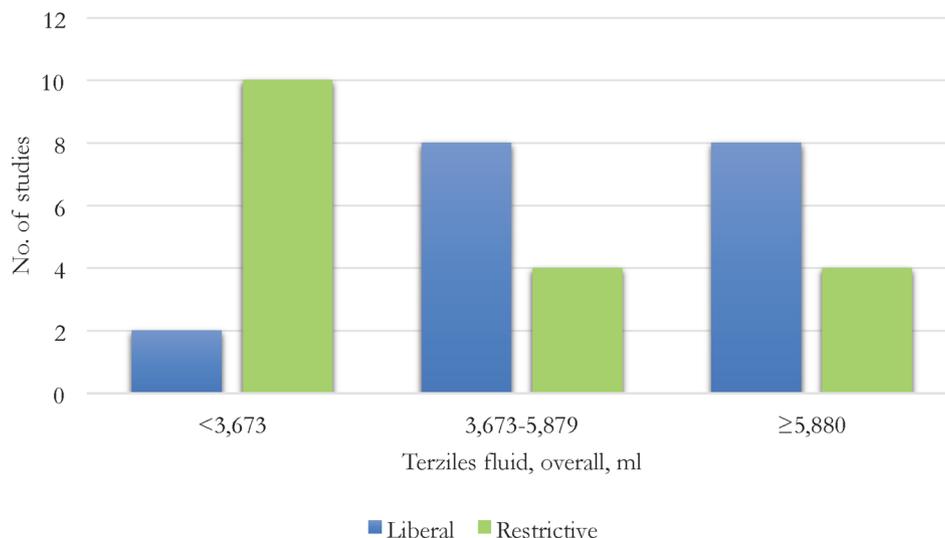


**Discussion**

This metaanalysis conducted on RCTs in major abdominal elective surgery regarding the effect of perioperative liberal or restrictive approach on postoperative outcomes

found no difference between the two approaches in the occurrence of the overall major postoperative complications or mortality. On the contrary, the liberal fluid policy

	Fluid, overall, reported days0-1, ml			p-value
	<3,673	3,673-5,879	≥5,880	
Mean (SD) major complications, %	36.1 (42.6)	19.0 (12.8)	27.7 (12.5)	0.35



**Fig. 5** Liberal / restrictive classification of the subgroups of patients in the included studies. Data are reported according to the tertiles of overall fluid amount (in ml) reported in the days 0 (day of the operation) and 1 (first postoperative day)

was associated with lower overall complication renal major events, as compared to the restrictive.

Postoperative complications are common after major surgery and represent a significant financial and social burden [2, 3]. Optimisation of fluid management has been extensively studied as a potentially modifiable peri-operative factor by adopting specific protocols focused on modality of fluid administration and cumulative fluid balance [9–11, 40]. The analysis of the literature in this field is rather complex due to the number of variables potentially affecting the final outcomes, which includes the overall complexity and the intrinsic risks of each specific type of the surgery.

On the one hand, a tendency towards a more restrictive approach (as supported by the ERAS pathways [13]) has been reported. In fact, a previous meta-analysis [19] showed that fewer patients had a lower total complication rate and risk of infection in the restrictive group as compared to the liberal group.

On the other, the recent large RCT performed by Myles et al. challenged this concept, showing that disability-free survival at 1 year did not change in patients randomised to a zero-balance vs a liberal approach, with the first strategy being associated with higher rates of acute kidney injury, surgical site infection and need for renal-replacement therapy [16]. Interestingly, this

single trial enrolled more patients than 17 RCTs combined in the previous 15 years (Table 1). The weight of this trial specifically impacts on postoperative major renal events of the present meta-analysis, which were lower in the liberal subgroup as compared to the restrictive (Fig. 4). Interestingly, renal events did not impact on overall mortality, despite the fact that acute kidney injury is recognised as an independent risk factor for mortality [41]. However, postoperative mortality is greatly affected by the results of the study of Myles et al. [16]. Moreover, the present meta-analysis did not include trials on cardiac surgery, which is a clinical setting specifically associated with an increased risk of death in those patients who develop postoperative acute kidney injury [41–43].

Considering the impact of crystalloids/colloids use on the renal postoperative outcome, this meta-analysis only suggests a possible additive effect of the colloids use in a restrictive approach. However, a recent large RCT comparing the use of low molecular weight hydroxyethyl-starch vs. 0.9% saline for intravascular volume expansion in high-risk surgical patients showed no significant difference in a composite outcome of death or significant postoperative [27]. For this reason, this result should be considered with extreme caution.

In the field of perioperative fluid administration, summarising the evidence available in the literature into straightforward clinical suggestions for daily clinical practice is rather complicated, and our updated results basically indicate an equivalence between the two perioperative fluid policies, suggesting a “third way”. The overall amount of fluid (perioperative target) should be integrated into an individualised goal-directed fluid replacement strategy (perioperative policy), to prevent fluid overload and fluid shortage by closely monitoring the effects of each bolus administered, as long as the individual plateau of the impact on predefined flow or pressure variables is achieved [12, 44]. Interestingly, this approach was incorporated into the intraoperative protocol of 5 studies [16, 25, 27–29], including the study of Myles et al. who assessed central venous pressure and stroke volume variation in case of intraoperative hypotension to guide resuscitation (supplementary appendix of the trial [16]). Moreover, a recent meta-analysis showed a trend towards the reduction of postoperative complications when a goal-directed therapy is used in patients receiving large amounts of perioperative fluids [45]. Thus, rather than choosing between a fixed-volume regimen and a goal-directed concept, an alternative approach could be to combine the two strategies. Of note, in the study of Myles et al. [16] restrictive fluid therapy had similar effects in patients treated with or without a goal-directed device.

As shown by our qualitative analysis, neither the perioperative intakes nor the fluid balance or the bodyweight gain has been consistently reported in the considered RCTs. Surprisingly, the overall fluid balance or the postoperative weight difference, which should be, in principle, the most effective perioperative variables depicting the fluid paths of restrictive and liberal subgroups, has been reported only in 5 studies (27.7%) [16, 33, 35, 46, 47]. The heterogeneity in actual overall fluid balance computation, as long the definition of postoperative complications (see further) greatly affects the comparability of the RCTs, soliciting clear standards in data reporting.

Considering the fluid intake alone, our data suggest that an overall median administration of about 4 L on days 0 and 1 may be considered restrictive, whereas about 6 L may be considered liberal. However, as pointed out by previous meta-analysis [18, 19], these cut-offs are associated with large inter-quartile ranges due to the lack of consistency in perioperative fluid regimen definition. Consequently, some subgroups of RCTs classified as restricted would be considered liberal in some other trials (see Fig. 5), because of overlapping perioperative volumes.

However, despite the lack of statistical significance, we found the highest rates of major complications in the highest and lowest tertiles of our sub-analysis.

Finally, the included studies all report overall low perioperative mortality rates; thus, as expected, the impact of liberal vs. restrictive strategies on perioperative mortality was not significant.

### Limitations

Some limitations of this study should be acknowledged.

First, as concern the data obtained from the included studies: 1) the definition of postoperative complications and the timing in mortality assessment may vary among the included studies, implying a bias in the reported outcomes' comparability. In fact, some complications (*i.e.* pneumonia, wound abscess/infection/dehiscence, pneumothorax) have been considered either as minor or major, according to study-specific criteria, which have been respected in the data analysis; 2) we computed major/minor complications according to either the criteria adopted in the study or (only for subgroup analysis) definitions clearly indicating the gravity degree (*i.e.* peritonitis and anastomotic leak has been always considered as severe complications); 3) the impact of restrictive/liberal policies on specific subgroups of patients is overall lacking (*i.e.* patients with pre-existing renal or diastolic cardiac dysfunction), limiting the generalisability of data; 4) this is not a meta-analysis based on individual data and the main author of each study (whenever needed) has been contacted only to provide more specific information regarding the results on the overall population enrolled. This is specifically important for colloids/crystalloids sub-analysis.

Third, the overall quality of the included studies reported “some concerns” in the majority of them (55.5%), mostly related to the selection of the reported results due to drawbacks in the trial registration. This is mainly due to the criteria imposed by the RoB 2 scale [22] for the trial registration. The International Committee of Medical Journal Editors policy regarding prospective trial registration was started in 2005 [48], and most of the trial published before 2010 do not fulfil the RoB 2 criteria for “low-risk” report. Moreover, a monitoring of the study protocol is reported only in three studies [16, 26, 33].

Finally, we adopted a database combination search strategy, including PUBMED®, EMBASE® and the Cochrane Controlled Clinical trials register, excluding different sources (*i.e.* Web of Science®). Although this choice should allow a reliable coverage of the published studies for the topic of interest, some RCTs could not be identified.

## Conclusions

In major abdominal elective surgery perioperative, the choice between liberal or restrictive approach did not affect overall major postoperative complications or mortality. In a subgroup analysis, a liberal fluid policy was associated with lower overall complication renal major events, as compared to the restrictive.

The lack of consistency in perioperative overall fluid balance and in the definitions of clinical outcomes still affects the comparability of the results of RTCs, soliciting clear standards in data reporting.

## Abbreviations

ASA: American Society of Anaesthesiologists (ASA) physical status score; RCT: Randomised controlled trial; ERAS: Enhanced recovery after surgery; SD: Standard deviation; 95%CI: 95% Confidence intervals.

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-021-03629-y>.

**Additional file 1.** Supplementary materials including supplementary tables and figures.

## Acknowledgements

None declared.

## Authors' contributions

A.M. and C.R. designed the study, conducted the primary data search, solved the classification discrepancies in data collection and drafted the manuscript; L.C., D.Z., F.I., E.M., S.S., D.B. and M.B. performed the evaluation of titles and abstracts and helped in data collection and the manuscript preparation, L.S. and G.S. conducted the data analysis and helped in manuscript preparation; P.P. substantially contributed in manuscript preparation and data interpretation; M.C. helped in designing the study and in the primary search and substantially contributed in manuscript preparation and data interpretation. All the authors approved the final version of the paper and agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Funding

This work has not been funded by an external source.

## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

Dr. Messina received travel expenses and registration for meetings, congresses, and courses and lecture fees from Vygon; Prof. Cecconi is a consultant for Edwards Lifesciences, LiDCO and Cheetah Medical.

## Author details

<sup>1</sup>Department of Anaesthesia and Intensive Care Medicine, Humanitas Clinical and Research Center – IRCCS, Via Alessandro Manzoni, 56, 20089 Rozzano, MI, Italy. <sup>2</sup>Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, MI, Italy. <sup>3</sup>Anaesthesia and Intensive Care, IRCCS for Oncology and Neuroscience, San Martino Policlinico Hospital, Genoa, Italy. <sup>4</sup>Department of Surgical Sciences and Integrated Diagnostic (DISC), University of Genoa, Genoa, Italy. <sup>5</sup>Anesthesia and Intensive Care Medicine, Maggiore Della Carità University Hospital, Novara, Italy. <sup>6</sup>Anesthesia and Intensive Care Medicine, Azienda Sanitaria Universitaria Integrata Udine, Udine, Italy. <sup>7</sup>Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental, University of Sassari, Sassari, Italy.

Received: 9 April 2021 Accepted: 6 June 2021

Published online: 11 June 2021

## References

- de Vries EN, Prins HA, Crolla RM, den Outer AJ, van Anel G, van Helden SH, et al. Effect of a comprehensive surgical safety system on patient outcomes. *N Engl J Med*. 2010;363:1928–37.
- Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242:326–41.
- Healy MA, Mullard AJ, Campbell DA Jr, Dimick JB. Hospital and payer costs associated with surgical complications. *JAMA Surg*. 2016;151:823–30.
- Kang SH, Lee Y, Min SH, Park YS, Ahn SH, Park DJ, et al. Multimodal enhanced recovery after surgery (eras) program is the optimal perioperative care in patients undergoing totally laparoscopic distal gastrectomy for gastric cancer: A prospective, randomized, clinical trial. *Ann Surg Oncol*. 2018;25:3231–8.
- Holte K, Kehlet H. Fluid therapy and surgical outcomes in elective surgery: a need for reassessment in fast-track surgery. *J Am Coll Surg*. 2006;202:971–89.
- Cecconi M, Corredor C, Arulkumaran N, Abuella G, Ball J, Grounds RM, et al. Clinical review: goal-directed therapy—what is the evidence in surgical patients? The effect on different risk groups. *Crit Care*. 2013;17:209.
- Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg*. 2011;112:1392–402.
- Lobo SM, de Oliveira NE. Clinical review: What are the best hemodynamic targets for noncardiac surgical patients? *Crit Care*. 2013;17:210.
- Marik PE. Perioperative hemodynamic optimization: a revised approach. *J Clin Anesth*. 2014;26:500–5.
- Voldby AW, Brandstrup B. Fluid therapy in the perioperative setting—a clinical review. *J Intensive Care*. 2016;4:27.
- 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;263:502–10.
- Heming N, Moine P, Coscas R, Annane D. Perioperative fluid management for major elective surgery. *Br J Surg*. 2020;107:e56–62.
- Gustafsson UO, Scott MJ, Schwenk W, Demartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced recovery after surgery (eras(r)) society recommendations. *World J Surg*. 2013;37:259–84.
- Miller TE, Myles PS. Perioperative fluid therapy for major surgery. *Anesthesiology*. 2019;130:825–32.
- Wrzosek A, Jakowicka-Wordliczek J, Zajackowska R, Serednicki WT, Jankowski M, Bala MM, et al. Perioperative restrictive versus goal-directed fluid therapy for adults undergoing major non-cardiac surgery. *Cochrane Database Syst Rev*. 2019;12:CD012767.
- Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. *N Engl J Med*. 2018;378:2263–74.
- Bundgaard-Nielsen M, Secher NH, Kehlet H. “Liberal” vs. “Restrictive” perioperative fluid therapy—a critical assessment of the evidence. *Acta Anaesthesiol Scand*. 2009;53:843–51.

18. Bundgaard-Nielsen M, Secher NH, Kehlet H. "Liberal" vs. "Restrictive" perioperative fluid therapy—a critical assessment of the evidence: review article. *Acta Anaesthesiol Scand*. 2009;53:843–51.
19. Schol PBB, Terink IM, Lancé MD, Scheepers HCJ. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. *J Clin Anesth*. 2016;35:26–39.
20. Pang Q, Liu H, Chen B, Jiang Y. Restrictive and liberal fluid administration in major abdominal surgery. *Saudi Med J*. 2017;38:123–31.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *BMJ*. 2009;339:b2535.
22. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. Rob 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898.
23. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. *BMJ*. 2008;336:1049–51.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557–60.
25. Matot I, Paskaleva R, Eid L, Cohen K, Khalailah A, Elazary R, et al. Effect of the volume of fluids administered on intraoperative oliguria in laparoscopic bariatric surgery: a randomized controlled trial. *Arch Surg*. 2012;147:228–34.
26. Kabon B, Akca O, Taguchi A, Nagele A, Jebadurai R, Arkilic CF, et al. Supplemental intravenous crystalloid administration does not reduce the risk of surgical wound infection. *Anesth Analg*. 2005;101:1546–53.
27. Futier E, Garot M, Godet T, Biais M, Verzilli D, Ouattara A, et al. Effect of hydroxyethyl starch vs saline for volume replacement therapy on death or postoperative complications among high-risk patients undergoing major abdominal surgery: the flash randomized clinical trial. *JAMA*. 2020;323:225–36.
28. 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.
29. Kassim D, Esmat I. Goal directed fluid therapy reduces major complications in elective surgery for abdominal aortic aneurysm: Liberal versus restrictive strategies. *Egypt J Anaesth*. 2016;32:167–73.
30. Gao T, Li N, Zhang JJ, Xi FC, Chen QY, Zhu WM, et al. Restricted intravenous fluid regimen reduces the rate of postoperative complications and alters immunological activity of elderly patients operated for abdominal cancer: A randomized prospective clinical trial. *World J Surg*. 2012;36:993–1002.
31. Grant F, Brennan MF, Allen PJ, DeMatteo RP, Kingham TP, D'Angelica M, et al. Prospective randomized controlled trial of liberal vs restricted perioperative fluid management in patients undergoing pancreatectomy. *Ann Surg*. 2016;264:591–8.
32. Kalyan JP, Rosbergen M, Pal N, Sargen K, Fletcher SJ, Nunn DL, et al. Randomized clinical trial of fluid and salt restriction compared with a controlled liberal regimen in elective gastrointestinal surgery. *Br J Surg*. 2013;100:1739–46.
33. Lavu H, Sell NM, Carter TI, Winter JM, Maguire DP, Gratch DM, et al. The hyslar trial: a prospective randomized controlled trial of the use of a restrictive fluid regimen with 3% hypertonic saline versus lactated ringers in patients undergoing pancreaticoduodenectomy. *Ann Surg*. 2014;260:445–53.
34. Piljic D, Petricevic M, Piljic D, Ksela J, Robic B, Klokocovnik T. Restrictive versus standard fluid regimen in elective minilaparotomy abdominal aortic repair-prospective randomized controlled trial. *Thorac Cardiovasc Surg*. 2016;64:296–303.
35. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE. Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: a randomized clinical trial. *Anesthesiology*. 2014;120:365–77.
36. Futier E, Constantin JM, Petit A, Chanques G, Kwiatkowski F, Flamein R, et al. Conservative vs restrictive individualized goal-directed fluid replacement strategy in major abdominal surgery: a prospective randomized trial. *Arch Surg*. 2010;145:1193–200.
37. Muller S, Zalunardo MP, Hubner M, Clavien PA, Demartines N. Zurich Fast Track Study G: a fast-track program reduces complications and length of hospital stay after open colonic surgery. *Gastroenterology*. 2009;136:842–7.
38. Abraham-Nordling M, Hjern F, Pollack J, Prytz M, Borg T, Kressner U. Randomized clinical trial of fluid restriction in colorectal surgery. *Br J Surg*. 2012;99:186–91.
39. Holte K, Foss NB, Andersen J, Valentiner L, Lund C, Bie P, et al. Liberal or restrictive fluid administration in fast-track colonic surgery: a randomized, double-blind study. *Br J Anaesth*. 2007;99:500–8.
40. Messina A, Pelaia C, Bruni A, Garofalo E, Bonicolini E, Longhini F, et al. Fluid challenge during anesthesia: a systematic review and meta-analysis. *Anesth Analg*. 2018.
41. See EJ, Jayasinghe K, Glassford N, Bailey M, Johnson DW, Polkinghorne KR, et al. Long-term risk of adverse outcomes after acute kidney injury: a systematic review and meta-analysis of cohort studies using consensus definitions of exposure. *Kidney Int*. 2019;95:160–72.
42. Wang Y, Bellomo R. Cardiac surgery-associated acute kidney injury: risk factors, pathophysiology and treatment. *Nat Rev Nephrol*. 2017;13:697–711.
43. Hobson CE, Yavas S, Segal MS, Schold JD, Tribble CG, Layon AJ, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119:2444–53.
44. Kampmeier TG, Ertmer C. Individualized goal-directed therapy: The challenge with the fluids. *Anesth Analg*. 2020;130:596–8.
45. Messina A, Robba C, Calabrò L, Zambelli D, Iannuzzi F, Molinari E, et al. Association between perioperative fluid administration and postoperative outcomes: a 20-year systematic review and a meta-analysis of randomized goal-directed trials in major visceral/noncardiac surgery. *Crit Care*. 2021;25:43.
46. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, 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;238:641–8.
47. van Samkar G, Eshuis WJ, Bennink RJ, van Gulik TM, Dijkgraaf MG, Preckel B, et al. Intraoperative fluid restriction in pancreatic surgery: a double blinded randomised controlled trial. *PLoS ONE*. 2015;10:e0140294.
48. De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the international committee of medical journal editors. *N Engl J Med*. 2004;351:1250–1.
49. Jie HY, Ye JL, Zhou HH, Li YX. Perioperative restricted fluid therapy preserves immunological function in patients with colorectal cancer. *World J Gastroenterol*. 2014;20:15852–9.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.