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REVIEW ARTICLE/BRIEF REVIEW

Restrictive fluid management strategies and outcomes in liver transplantation: a systematic review

Stratégies de prise en charge liquidienne restrictive et pronostics en transplantation hépatique : une revue systématique

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Abstract

Purpose *Restrictive fluid management strategies have been proposed to reduce complications in liver transplant recipients. We conducted a systematic review to evaluate the effects of restrictive perioperative fluid management strategies, compared with liberal ones, on postoperative outcomes in adult liver transplant recipients. Our primary outcome was acute kidney injury (AKI). Our secondary outcomes were bleeding, mortality, and other postoperative complications.*

Source *We searched major databases (CINAHL, EMB Reviews, EMBASE, MEDLINE, and the grey literature) from their inception to 10 July 2018 for randomized-controlled trials (RCTs) and observational studies comparing two fluid management strategies (or observational studies reporting two outcomes with available data on fluid volume received) in adult liver transplant recipients. Study selection, data abstraction, and risk of bias assessment were performed by at least two investigators. Data from RCTs were pooled using risk ratios (RR) and mean differences (MD) with random-effect models.*

Principal findings *We found seven RCTs and 29 observational studies. Based on RCTs, fluid management*

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strategies did not have any effect on AKI, mortality, or any other postoperative complications. Intraoperative RCTs suggested that a restrictive fluid management strategy reduced pulmonary complications (RR, 0.69; 95% confidence interval [CI], 0.47 to 0.99; n = 283; I^2 = 27%), duration of mechanical ventilation (MD, -13.04 hr; 95% CI, -22.2 to -3.88; n = 130; I^2 = 0%) and blood loss (MD, -1.14 L; 95% CI, -1.72 to -0.57; n = 151; I^2 = 0%).

Conclusion *Based on low or very low levels of evidence, we did not find any association between restrictive fluid management strategies and AKI, but we observed possible protective effects of intraoperative restrictive fluid management strategies on other outcomes.*

Trial registration *PROSPERO (CRD42017054970); registered 18 May, 2017.*

Résumé

Objectif *Des stratégies de prise en charge liquidienne restrictives ont été proposées afin de réduire les complications chez les récipiendaires de transplantation hépatique. Nous avons réalisé une revue systématique visant à évaluer les effets des stratégies de prise en charge liquidienne périopératoire restrictives, par rapport à des stratégies libérales, sur les pronostics postopératoires des récipiendaires adultes de transplantation hépatique. Notre critère d'évaluation principal était l'insuffisance rénale aiguë (IRA). Nos critères secondaires étaient les saignements, la mortalité et les autres complications postopératoires.*

Source *Nous avons effectué des recherches dans les principales bases de données (CINAHL, revues EMB, EMBASE, MEDLINE, et littérature grise) de leur création jusqu'au 10 juillet 2018 afin d'en extraire les études randomisées contrôlées (ERC) et les études observationnelles comparant deux stratégies de prise en charge liquidienne (ou les études observationnelles rapportant deux critères d'évaluation et comportant des données disponibles sur les volumes liquidiens reçus) chez les récipiendaires adultes de transplantation hépatique. La sélection des études, l'extraction des données et l'évaluation du risque de biais ont été réalisées par au moins deux chercheurs. Les données tirées des ERC ont été pondérées à l'aide de rapports de risque (RR) et des différences des moyennes (DM) avec des modèles à effets aléatoires.*

Constatations principales *Nous avons retenu sept ERC et 29 études observationnelles. Selon les ERC, les stratégies de prise en charge liquidienne n'ont eu aucun effet sur l'IRA, la mortalité, ou toute autre complication postopératoire. Selon les ERC intraopératoires, les stratégies de prise en charge liquidienne restrictives réduisaient les complications pulmonaires (RR, 0.69; intervalle de confiance [IC] 95 %, 0,47 à 0,99; n = 283; I^2 = 27 %), la durée de la ventilation mécanique (DM, -13,04 h; IC 95 %, -22,2 à -3,88; n = 130; I^2 = 0 %) et les pertes sanguines (DM, -1,14 L; IC 95 %, -1,72 à -0,57; n = 151; I^2 = 0 %).*

Conclusion *En se fondant sur des niveaux de données probantes faibles ou très faibles, nous n'avons trouvé aucune association entre des stratégies de prise en charge liquidienne restrictives et l'IRA, mais avons observé des effets protecteurs possibles de stratégies de prise en charge liquidienne restrictive intraopératoires sur d'autres pronostics.*

Enregistrement de l'étude *PROSPERO (CRD42017054970); enregistrée le 18 mai 2017.*

Liver transplantation is the only effective therapy for severe end-stage liver disease and is increasingly performed throughout the world.[1,2] On average, liver transplant recipients suffer from more than three early postoperative complications (renal, pulmonary, and infectious being the most common), with over half of them being severe.[3,4] Perioperative variables, including hemodynamic variations and transfusion volume, have been associated with these complications.[5-11] Nevertheless, very few interventions are known to decrease their incidence.[12,13]

A recent clinical trial conducted in adult patients undergoing major abdominal surgery showed that a fixed restrictive fluid management strategy was associated with an increased risk of acute kidney injury (AKI).[14] On the other hand, evidence from systematic reviews of a wide range of surgical procedures (including abdominal surgery) suggest that the use of restrictive or cardiac output-guided perioperative fluid management strategies improve postoperative outcomes.[15-18] None of the latter studies or systematic reviews included liver transplant recipients and no such high-quality data are available in this population.[19] Despite the uncertain level of evidence, restrictive fluid management strategies including phlebotomies, normovolemic hemodilution, and conservative volume of fluid administration have been recommended to improve the outcome in this population.[20-22]

Considering the growing use of restrictive fluid management strategy in liver transplant recipients, it behooves us to understand its impact on the risk of postoperative complications.[20,21] As such, we conducted a systematic review on the effects of restrictive fluid management strategies compared with liberal ones on clinically important outcomes in adult liver transplant recipients.

Methods

We designed this systematic review according to the standard methodology developed by the Cochrane Collaboration[23] and reported the results according to the PRISMA statement.[24] We previously published its protocol.[25]

Search strategy and information sources

We developed a search strategy that incorporated key words *liver transplantation* and *fluid therapy*. We used key words from controlled vocabulary (MESH, EMTREE, and others) and free text searching (see Electronic Supplementary Material [ESM]). We searched the following databases: CINAHL Complete, EMB Reviews, EMBASE, MEDLINE from inception up to 10 July 2018, as well as the grey literature (CADTH, Clinical Trials, National Guideline Clearing House, NICE, MedNar, Google Scholar, and Open Grey). We searched for other studies within the references of selected studies. We searched for relevant abstracts published in the annual meeting supplements of the following organizations for the years available on their website: American Association for the Study of Liver Diseases, European Association for the Study of Liver, International Liver Transplantation Society, American Society of Transplantation, and European Society of Organ Transplantation.

Study eligibility

Participants

We included studies conducted in adults (defined as more than 80% of participants of $\geq$ 18 yr old or as defined in individual studies) undergoing liver transplantation. We excluded studies with more than 20% of the patients receiving another concurrent solid organ transplantation (kidney, lung, or heart).

Intervention

We considered any restrictive fluid management strategy, defined as any fluid management strategy or protocol that limited the amount of administered fluid, instituted in the intraoperative and/or postoperative period (e.g., restrictive early-goal directed protocols, restrictive weight-based protocols, low-central venous pressure [CVP] protocols, phlebotomies, restrictive fixed volume management protocols, retrospectively restrictive classified groups, etc.).

Comparator

We considered any fluid management strategy that was more liberal than the intervention.

Outcomes

Our primary efficacy outcome was the incidence of acute kidney injury (AKI), as defined by authors (any definition) up to 30 postoperative days. Our secondary outcomes were mortality (hospital and latest in time reported), pulmonary complications (pneumonia, pulmonary edema, acute respiratory distress syndrome), duration of mechanical ventilation (MV) (or ventilation-free days at latest in time reported), graft complications (graft failure, biliary leak, strictures and/or post-transplant cholangiopathy), cardiovascular complications (myocardial infarction, arrhythmias, shock, thromboembolic events), non-pulmonary infections, intraoperative bleeding, intensive care unit (ICU) length of stay (LOS), ICU readmission, and hospital LOS (any definition). We selected AKI as a primary patient-centred outcome because of its high incidence (between 13% and 71 %) and its association with both intraoperative and postoperative outcomes such as mortality and burden of care.[3,4,8,9,26,27]

Types of studies

We included randomized-controlled trials (RCTs), quasi randomized trials, and comparative non-randomized studies (prospective or retrospective). Studies were considered if at least two different fluid management strategies were compared, one being more restrictive than the other, or if at least two different volumes of fluid were administered. Observational studies were also included if the volume of fluid received could be extracted from at least two different outcome-based groups categorized on one of our outcomes of interest

Study selection and data extraction

We used Endnote X8.2 software to merge retrieved titles, remove duplicates, and screen titles and abstracts. Four investigators independently selected potentially eligible studies (F.M.C. and a second reviewer (P.A., M.C., or S.I.). Two investigators (F.M.C., M.C.) did a full-text review of selected citations to confirm their eligibility. Studies in a language other than French or English were translated before data extraction. We contacted authors for additional information when deemed necessary for inclusion (missing data on outcome or exposure); no author answered our queries. Two investigators (F.M.C. and H.T.W.) independently extracted data from included studies using a standardized

electronic data extraction form that included study and population characteristics, intraoperative and postoperative type and volume of fluid received, bleeding, the amount of blood products transfused, major co-interventions and every reported outcome relevant to this review (see ESM). Disagreements were resolved by consensus.

Risk of bias assessment

For RCTs, we assessed the risk of bias (RoB) using the Cochrane RoB 2.0 assessment tool for our primary outcome (AKI), or the primary outcome of the study itself if AKI was not reported.[28] For cohort studies, we used the same approach for both exposure-based (intervention *vs* control) and outcome-based studies (patients with the outcome *vs* patients without the outcome) and assessed RoB for the primary outcome of the study (or AKI if no primary outcome was mentioned) with the ROBINS-I tool.[29] We classified any reported association without adjustment for confounders as "critical" in the "confounding" domain and all outcome-based cohort studies as "critical" for the "classification of intervention" domain. Two investigators (F.M.C. and H.T.W.) independently assessed the RoB for all studies. Disagreements were resolved by consensus. Risk of bias was used for some subgroup analyses and for the GRADE summary of findings table. We planned to assess publication bias by funnel plots if more than ten manuscripts were included per outcome.[23]

Data synthesis

We quantitatively pooled data from RCTs. We calculated risk ratios (RR) with 95% confidence intervals (CI) using the Mantel-Haenszel method for dichotomous outcomes and mean differences (MD) with 95% CI using the inverse variance method for continuous outcomes. We used reported medians in pooled analyses and calculated standard deviations (SD) by dividing the interquartile range [IQR] by 1.35. Means were reported with SD and medians with IQR. We used random-effect models to consider the underlying variation across studies. We reported the I^2 measure of consistency to evaluate statistical heterogeneity. We performed three subgroup analyses: period of interventions (intraoperative *vs* postoperative), subtypes of interventions (studies using low CVP as the restrictive fluid management strategy *vs* others) and studies' RoB (high *vs* low or some concerns of RoB). We also performed sensitivity analyses by removing studies reporting a median and by using a Bonferonni correction to adjust for the multiple statistical tests we performed through secondary outcome analyses (eight statistical tests using 99.4% CI). For observational studies, we calculated individual odds ratios (OR) with 95% CI and MD with 95% CI for continuous outcomes. We performed statistical analyses in Review Manager 5.3 (The Cochrane Collaboration, 2014) and R (version 3.5.2). We generated a summary of findings table with the quality of cumulative evidence according to GRADE criteria with the GRADEpro web-based tool (gradepro.org).[30]

Results

A flowchart of the study selection is presented in Fig. 1. The studies and population characteristics are summarized in Table 1 and eTable 1 (available as ESM), and the RoB assessment is summarized in Fig. 2. We could not assess publication bias because the number of included studies was too low.

We found seven RCTs meeting our eligibility criteria.[31-37] We considered five of them at high RoB.[32,34-37] Five RCTs[31-35] were conducted in the intraoperative period: four of them used a low-CVP goal as the restrictive fluid management strategy[31,32,34,35] and one used a strategy based on vasopressor use (norepinephrine *vs* placebo) to restrict fluid intake.[33] Two RCTs were conducted in the postoperative period[36]: one compared CVP with stroke volume or right ventricular end diastolic volume as variables to guide fluid administration[36]; the other study compared the administration of albumin with usual care.[37] Populations were comparable among RCTs, except one study[34] that included patients with more severe liver failure than other studies (eTable 1 as ESM).

We found 29 observational cohort studies,[38–66] with all except two studies[40,43] being considered at high or critical RoB. Among the 14 exposure-based cohort studies,[38-51] nine collected data from the intraoperative period: three compared low CVP with another strategy (one compared two centres using different protocols[38]; one compared two groups retrospectively classified as to CVP values after reperfusion[39]; and one compared low CVP with goal-directed therapy in a before-after study)[40]; one compared stroke volume variation (SVV) goal-directed therapy with high-CVP management[41]; two from the same centre compared the use of phlebotomies with either unmatched historical controls (before-after study)[42] or contemporary controls[43]; two compared two retrospectively classified groups (one based on SVV[44] and one based on the volume of fluid received)[45]; and one compared two groups in a before-after study (practice changed over time toward a more restrictive approach).[46] Three studies collected data for the complete perioperative period (intraoperative and postoperative periods): two before-after studies compared patients receiving a restrictive fluid management (either restrictive goal-directed therapy[47] or a fast-track bundle

that included restricting fluid)[48] with unmatched historical controls and one compared two retrospectively classified albumin-treated groups.[49] Two before-after studies collected data during the postoperative period: one compared albumin administration to no administration[50] and one compared patients receiving a goal-directed therapy to unmatched historical controls.[51] For the 15 outcome-based cohort studies,[52-66] we compared volumes of fluid received between reported groups in each outcome section. The volume of fluid received, the amount of blood products transfused, and other co-interventions are presented in eTable 2a–c (available as ESM).

We summarized results by outcomes. Individual study results and RCTs' pooled results are reported in eTable 2 and eTable 3a–j (ESM) and Fig. 3 and eFig. 1 (ESM). Subgroup and sensitivity analyses are reported in eFig. 2 and eFig. 3 (ESM).

Acute kidney injury (AKI)

Four out of seven RCTs reported data on AKI.[31,35-37] Data pooling was not possible because of outcome heterogeneity. One study did not show any difference in the risk of developing postoperative AKI without providing any definition (RR, 0.88; 95% CI, 0.35 to 2.20; $n = 86$)[31] and one study reported no need for postoperative renal replacement therapy (RRT) in either group.[35] One intraoperative RCT[35] and two postoperative RCTs[36,37] reported creatinine levels and did not show any difference between groups (Table 2).

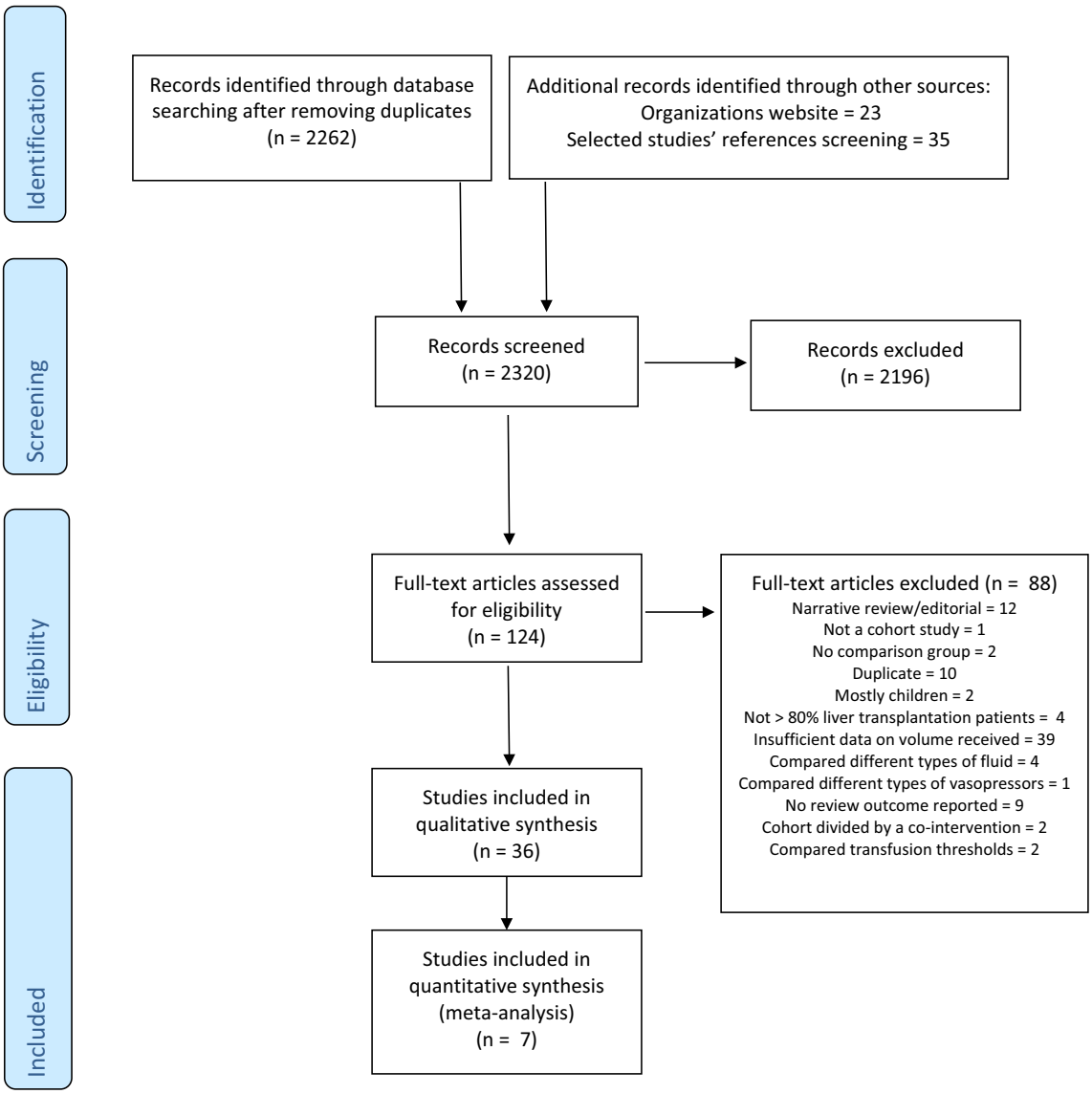


Fig. 1 PRISMA flow diagram of retrieved articles

TABLE 1a Characteristics of included randomized-controlled trials

Author	Year	Country	Period of inclusion	Intervention (restrictive)	N	Control (liberal)	N	Primary outcome	Secondary outcomes
Intraoperative period of intervention									
Sahmeddini(1) (35)	2014	Iran	02/2010–11/2010	Restrictive fluid management (crystalloid baseline infusion of 5 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ + CVP between 8 and 10 mmHg)	34	Liberal fluid management (crystalloid baseline infusion of 10 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ + CVP > 10 mmHg)	33	AKI with RRT & acute respiratory insufficiency with MV	Pulmonary edema, ICU LOS
Sahmeddini(2) (32)	2014	Iran	02/2010–09/2010	Restrictive fluid management (crystalloid baseline infusion of 5 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ + CVP ≥ 80% baseline) up to the reperfusion phase	37	Liberal fluid management (crystalloid baseline infusion of 10 $mL{\cdot}kg^{-1}{\cdot}hr^{-1}$ + CVP ≥ 80% baseline) up to the reperfusion phase	38	Dosage of $NaHCO_3$ used	Blood loss
Wang (34)	2013	China	06/2003–12/2010	Low CVP (< 5 mmHg or reduced by 40%)	33	Usual care (CVP 8–10 mmHg)	32	Pulmonary complications	Blood loss, 1-year mortality, 1-year graft function
Feng (31)	2010	China	09/2006–01/2008	Low CVP (< 5 mmHg or reduced by 40%) during dissection phase	43	Usual care	43	Blood loss	AKI, AKI with RRT, pulmonary complications, graft failure, infections, ICU LOS, hospital LOS
Ponnudurai (33)	2005	USA	NA	Norepinephrine-based fluid restriction (blinded)	33	Usual care with placebo infusion	32	PO reintubation	Pulmonary edema, duration of MV, ICU LOS, hospital LOS
Postoperative period of intervention									
Yassen (36) (3 arm study)[1]	2012	Egypt	10/2007–01/2011	CVP-guided (> 4 mmHg) fluid management	17	SV-guided (> 55 $mL{\cdot}m^{-2}$) fluid management RVEDVI-guided (> 110 $mL{\cdot}m^{-2}$) fluid management	18 18	Fluid requirement in the first 3 PO days[3]	Creatinine concentration, pulmonary complications, graft failure, infections, duration of MV, ICU LOS, 3-month mortality
Mukhtar (37)	2007	Egypt	NA	Usual care	20	20% albumin infusion (to maintain albumin level > 30 g/L)	20	Fluid requirement in the first 5 PO days[3]	Creatinine concentration, duration of MV, infections, ICU LOS, hospital LOS

AKI = acute kidney injury; ALF = acute liver failure; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVP = central venous pressure; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; ICU = intensive care unit; LOS = length of stay; LT = liver transplantation; MV = mechanical ventilation; PACU = postanesthesia care unit; PE = pulmonary edema; PO = postoperative; RBC = red blood cells; RoB = risk of bias; RRT = renal replacement therapy; RVEDVI = right ventricular end diastolic volume index; SOFA = Sequential Organ Failure Assessment; SV = stroke volume; SVV = stroke volume variation

[1] This study is a three-arm study. We combined the two more liberal groups together for all analyses

Seven exposure-based (restrictive *vs* liberal fluid management) observational cohort studies reported data on AKI (Table 2).[38,40-42,44,49,67] Three intraoperative studies and one perioperative study did not show any effect.[41,44,49,67] One study reported that a restrictive strategy significantly increased the need for RRT (not supported by our calculated OR; see Table 2).[38] One before-after intraoperative study showed a higher incidence of AKI in the restrictive group

TABLE 1b Characteristics of included exposure-based observational cohort studies

Author	Year	Country	Period of inclusion	Intervention group (restrictive)	N	Control group (liberal)	N	Primary outcome[1]	Other reported outcomes (descriptive analysis)
Intraoperative period of intervention									
Fayed (40)	2017	Egypt	07/2011–10/2014	Low CVP (40% lower than baseline) during dissection phase (2011–2012)	45	Doppler goal-directed therapy (FTc > 0.35) for the whole procedure (matched, 2012–2014)	45	Blood loss	AKI, AKI with RRT, 3-month mortality
Choi (44)	2016	Korea	12/2009–12/2013	Retrospectively classified high SVV (10–20%)	44	Retrospectively classified low SVV (< 10%)	288	AKI	ICU LOS, hospital LOS, 1-year mortality
Massicotte[2] (43)	2015	Canada	10/2002–06/2015	Phlebotomy (7–10 mL·kg^{-1}) before dissection up to reperfusion	406	No phlebotomy	294	Blood loss	1-year mortality
Lekerika (45)	2014	Spain	01/2010–12/2011	Retrospectively classified restrictive volume management	45	Retrospectively classified liberal volume management	44	Intraoperative transfusions[3]	AKI, AKI with RRT, pulmonary complications, graft complications, ICU LOS, hospital LOS, 30-day mortality
Wang (41)	2012	Taiwan	2007–2011	SVV ≤ 10% guided fluid management	25	CVP 8–10 mmHg guided fluid management	25	AKI	Blood loss, 30-day & 1-year mortality
Cywinski (39)	2010	USA	05/2005–12/2006	Retrospectively classified CVP < 10 mmHg after reperfusion	56	Retrospectively classified CVP > 10 mmHg after reperfusion	88	Survival time up to 2 years	Blood loss, graft failure, ICU LOS, hospital LOS
Massicotte (42)	2006	Canada	1998–2003	Low CVP (40% lower than baseline with or without a phlebotomy) up to reperfusion	98	Historical controls	206	Blood loss	Postoperative creatinine, hospital LOS, 1-year mortality
Nemes[4] (46)	2005	Hungary	1995–2004	2003–2004: less transfusions and colloids	NA	1995–2002	NA	Infections	
Schroeder (38)	2004	USA (2 sites)	1998–2001	Low-CVP management centre (< 5 mmHg) up to reperfusion	73	Normal CVP management centre (no goal)	78	AKI with RRT	Graft failure, ICU LOS, hospital LOS, 30-day mortality
Intraoperative and postoperative periods of intervention									
King (48)	2018	USA	11/2012–10/2014	Fast-track protocol (2013–2014)	141	Historical control (2012–2013)	106	ICU LOS	Hospital LOS, ICU readmissions, hospital mortality
Reydellet (47)	2014	France	06/2010–06/2011	Restrictive goal-directed algorithm therapy (01 to 06/2011)	25	Historical control (06 to 12/2010)	25	Fluid balance[4]	Duration of MV, graft complications, ICU LOS, hospital LOS, ICU mortality, 28-day mortality
Johnson (49)	2006	USA	01/2003–12/2003	Retrospectively classified low albumin volume received (< median)	20	Retrospectively classified high albumin volume received (> median)	20	Total morbidity[4]	AKI, graft failure, CV complications, infections, 6-month mortality

TABLE 1b continued

Author	Year	Country	Period of inclusion	Intervention group (restrictive)	N	Control group (liberal)	N	Primary outcome[1]	Other reported outcomes (descriptive analysis)
Postoperative period of intervention									
Ertmer (50)	2015	Germany	01/2010–03/2012	Historical control (01/2010–07/2010)	15	100 g/day of 20% albumin for 7 days (08/2010– 03/2010)	15	SOFA score[4]	ICU LOS, ICU mortality, 1-year mortality, survival time up to 1 year
Takeda (51)	2015	Japan	NA	SVV < 10% fluid management (prospective)	9	CVP > 10 mmHg fluid management (historical)	52	Duration of MV	Blood loss, time to extubation

AKI = acute kidney injury; ALF = acute liver failure; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVP = central venous pressure; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; ICU = intensive care unit; LOS = length of stay; LT = liver transplantation; MV = mechanical ventilation; PACU = postanesthesia care unit; PE = pulmonary edema; PO = postoperative; RBC = red blood cells; RoB = risk of bias; RRT = renal replacement therapy; RVEDVI = right ventricular end diastolic volume index; SOFA = Sequential Organ Failure Assessment; SV = stroke volume; SVV = stroke volume variation

[1] The study's primary outcome was used to assess RoB for observational studies. If no primary outcome is mentioned in the article, we used AKI to assess RoB

[2] Includes all patients from the intervention group of the 2006 study. Both studies are reported, because the 2006 study reports patients exposed to a bundle compared with historical controls and the 2015 study compares patients with or without a specific intervention within the bundle (phlebotomy)

[3] Not included in this review's outcomes but used to assess risk of bias

[4] Translated from Hungarian. Authors did not report the number of patients per group, but reported a total of 358 patients for both groups

TABLE 1c Characteristics of included outcome-based observational cohort studies

Author	Year	Country	Period of inclusion	Main outcome (groups)	N with outcome	N without outcome	Data on fluid management	Other reported outcomes by groups (not analyzed)
Intraoperative period of intervention								
Massicotte[1] (66)	2018	Canada	10/2002–02/2016	Bleeding < or > 900 mL (median)	420	379	Intraoperative fluids, intraoperative transfusions and % of patients who had a phlebotomy	
Jipa (58)	2017	Romania	01/2014–04/2014	Pulmonary complications *vs* no complication	23	17	Intraoperative fluids and transfusions	Blood loss, PACU LOS
Chan (59)	2017	Taiwan	02/2004–10/2008	ARDS *vs* no ARDS	24	81	Intraoperative fluids and transfusions	Blood loss, duration of MV, ICU LOS, hospital LOS, 1-year mortality, 5-year mortality
Garutti (64)	2015	Spain	03/2011–12/2013	Postoperative MV < 48 hr *vs* MV > 48 hr	12	81	Intraoperative fluids and transfusions	Graft function, duration of MV, ICU LOS, hospital LOS, 30-day mortality
Jiang (60)	2012	China	07/1996–07/2009	Pulmonary complications *vs* no complication	47	55	Intraoperative fluids and transfusions	Blood loss, time to extubation[4], ICU LOS[4]

TABLE 1c continued

Author	Year	Country	Period of inclusion	Main outcome (groups)	N with outcome	N without outcome	Data on fluid management	Other reported outcomes by groups (not analyzed)
Lin (61)	2010	China	04/2007–03/2009	Pulmonary complications *vs* no complication	65	42	Intraoperative fluids and transfusions	Need for MV, mortality (unknown timeline)
Kundakci (55)	2010	Turkey	01/2000–02/2009	AKI *vs* no AKI	64	48	Intraoperative fluids and transfusions	ICU LOS, hospital LOS, 1–year mortality
Niemann (57)	2009	USA (two sites)	10/2007–10/2008	AKI *vs* no AKI	27	32	Intraoperative fluids and transfusions	ICU LOS, hospital LOS
O'Riordan (56)	2007	Ireland (multi-centred)	01/1993–07/2004	AKI (2 levels) *vs* no AKI	129	221	Intraoperative fluids and transfusions	Blood loss, graft complications, sepsis, hospital LOS
Neelakanta (65)	1997	USA	07/1994–08/1995	Early extubation *vs* late extubation	17	18	Intraoperative fluids and transfusions	ICU LOS, hospital LOS
Intraoperative and postoperative periods of intervention								
Codes (52)	2018	Brazil	NA	AKI *vs* no AKI	87	34	Intraoperative transfusions, PO fluid balance up to 4 days	Sepsis, graft complications, ICU LOS, hospital LOS, 28-day mortality
Nadeem (54)	2014	Saudi Arabia	01/2010–09/2013	AKI *vs* no AKI	57	101	Intraoperative and PO fluids and transfusions up to 72 hours, intraoperative and PO fluid balance up to 24 hours	Duration of MV, ICU LOS
Aduen (62)	2003	USA	02/1998–10/1999	Late PE *vs* early PE *vs* persistent PE *vs* no PE	47	44	Intraoperative and PO fluids and transfusions up to 24 hours	Duration of MV, ICU LOS, hospital LOS, 28-day mortality
Snowden (63)	2000	UK	NA	Late PE *vs* early PE *vs* no PE	16	18	Intraoperative albumin and blood product transfusions, PO crystalloids and colloids	Blood loss, duration of MV, ICU LOS
Postoperative period of intervention								
Haddad (53)	2014	Brazil	01/2011–12/2012	AKI with RRT *vs* no RRT	51	128	PO water balance up to 1 day	Mortality (unknown timeline)

AKI = acute kidney injury; ALF = acute liver failure; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVP = central venous pressure; ESLD = end-stage liver disease; HCC = hepatocellular carcinoma; ICU = intensive care unit; LOS = length of stay; LT = liver transplantation; MV = mechanical ventilation; PACU = postanesthesia care unit; PE = pulmonary edema; PO = postoperative; RBC = red blood cells; RoB = risk of bias; RRT = renal replacement therapy; RVEDVI = right ventricular end diastolic volume index; SOFA = Sequential Organ Failure Assessment; SV = stroke volume; SVV = stroke volume variation

[1] Includes all patients from the 2015 study plus 100 new patients

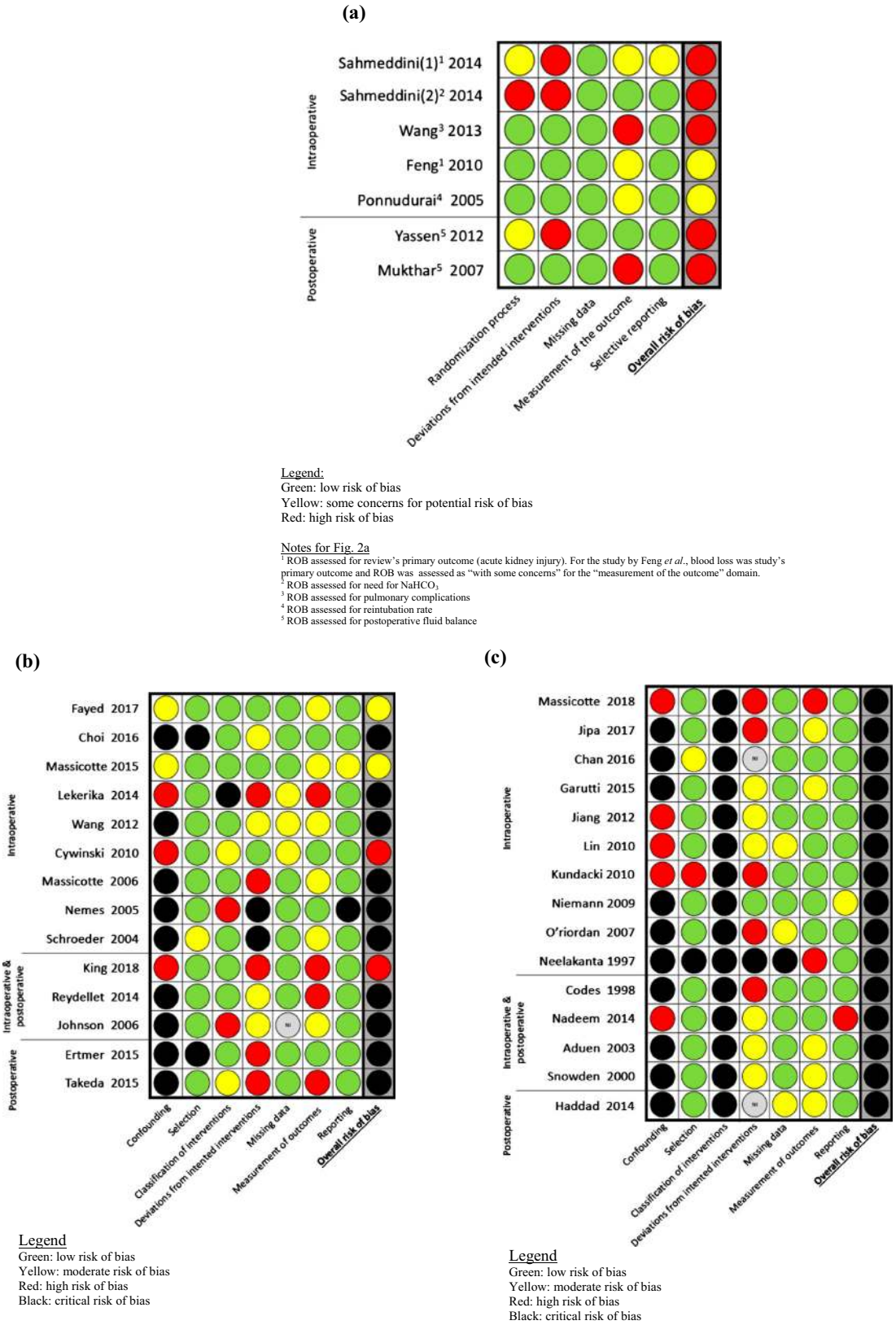


Fig. 2 Risk of bias assessment. a Risk of bias for RCT (RoB 2.0 tool). b Risk of bias for exposure-based observational studies (ROBINS-I tool). c Risk of bias for outcome-based observational studies (ROBINS-I tool)

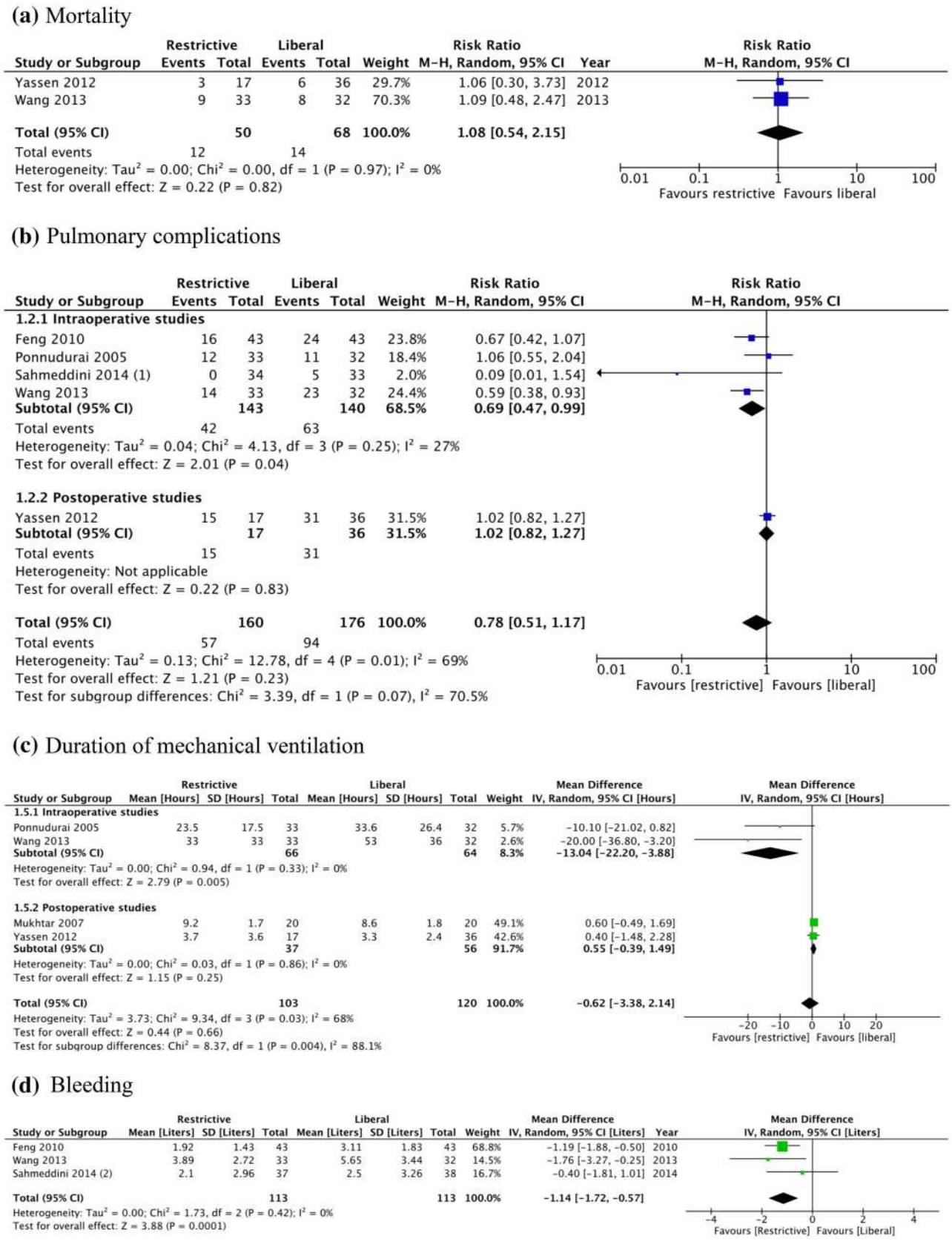
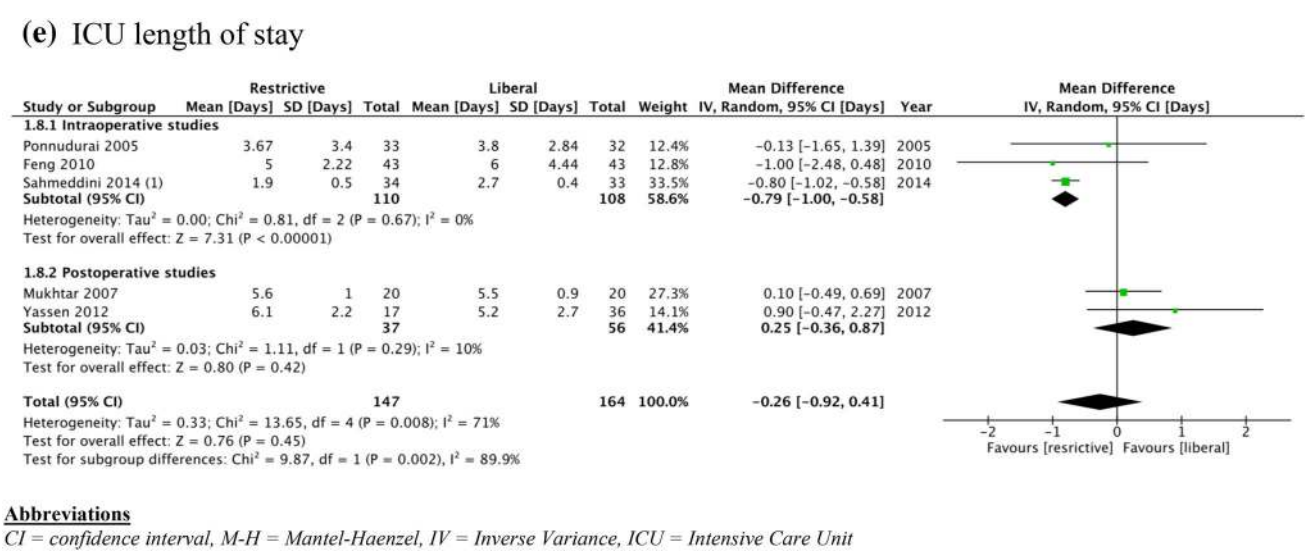


Fig. 3 Meta-analyses results. a Mortality. b Pulmonary complications. c Duration of mechanical ventilation. d Bleeding. e ICU length of stay. CI = confidence interval; M-H = Mantel-Haenzel; ICU = intensive care unit; IV = inverse variance; RCT = randomized-controlled trial



Abbreviations

CI = confidence interval, M-H = Mantel-Haenzel, IV = Inverse Variance, ICU = Intensive Care Unit

Fig. 3 continued

(the "before" group), without increased need for RRT.[40] One before-after study reported similar creatinine levels at postoperative day 1, but lower levels in the restrictive group (the "after" group) on postoperative day 3.[42]

Six studies used AKI as an outcome to categorize their cohort.[52-57] One intraoperative study did not show any difference on the volume received between groups[56] and two intraoperative studies reported similar intraoperative mean crystalloid volumes but different intraoperative mean (SD) colloid volumes between groups [307 (438) mL AKI *vs* 102 (202) mL no AKI, $P = 0.005$; 2259 (1382) mL AKI *vs* 1453 (1618) mL, no AKI $P = 0.06$].[55,57] One perioperative study also showed higher median [IQR] colloid volumes in the AKI group (2100 [0–4600] mL (AKI) *vs* 1500 [500–2500] mL (no AKI) of intraoperative colloid ($P = 0.01$), and 3850 *vs* 2000 mL of postoperative colloid, respectively, no P value).[54] Finally, one study reported a higher mean (SD) fluid balance at postoperative day 4 in patients with AKI [11841 (5395) mL (AKI) *vs* 8690 (3463) mL no (AKI), $P = 0.05$][52] and one study reported a higher mean (SD) postoperative water balance at day 1 in patients with AKI requiring RRT [2735 (2139) mL (AKI) *vs* 1711 (1763) mL (no AKI), $P = 0.01$][53] (eTable 2c).

Mortality

Two RCTs reported mortality (eTable 3a).[34,36] Pooled data from reported mortality, the latest available in each study, did not suggest any effect (RR, 1.08; 95% CI, 0.54 to 2.15, $n = 118$, $I^2 = 0\%$) (Fig. 3a). Of these two RCTS, the one performed in an intraoperative setting reported no deaths at 1 month and a comparable one-year mortality between groups (RR, 1.09; 95% CI, 0.48 to 2.47; one study, $n = 65$).[34] The second RCT performed during the postoperative period reported a comparable three-month mortality between three different groups.[36] Among the twelve cohort studies reporting data on mortality, eleven studies did not show any effect[38–42,44,47-50,67] and one study reported a lower one-year mortality with the use of intraoperative phlebotomy as part of a restrictive strategy (OR, 0.50; 95% CI, 0.27 to 0.92)[43] (eTable 3a).

Pulmonary complications

Four intraoperative RCTs reported pulmonary complications either as a category or separately (pulmonary edema, pneumonia or pleural effusion)[31,33-35] and one postoperative RCT reported incidence of pleural effusions.[36] Pooled data did not suggest any effect of fluid management on pulmonary complications (RR, 0.78; 95% CI, 0.51 to 1.17; five studies; $n = 336$; $I^2 = 69\%$)[31,33–36] (Fig. 3b). In our first subgroup analysis, intraoperative restrictive fluid management strategies decreased the risk of pulmonary complications (RR, 0.69; 95% CI, 0.47 to 0.99; four studies; $n = 283$; $I^2 = 27\%$)[31,33-35] (Fig. 3b). No effect in either RoB group (high, some concerns) was observed (eFig. 2a). Nevertheless, we observed an effect of intraoperative low-CVP management (RR, 0.61; 95% CI, 0.44 to 0.85; three studies; $n = 218$; $I^2 = 3\%$)[31,34,35] (eFig. S2b). These subgroup analyses also identified variables, such the period of intervention, that accounted for the statistical heterogeneity (see Fig. 3a and eFig. 1a–b).

TABLE 2 Acute kidney injury outcome results of included observational studies

RCT					
Author	RoB	Restrictive group	Liberal group		RR with 95% CI
AKI					
Feng (31)	Some concerns	7/43	8/43		0.88, 0.35 to 2.20
Sahmeddini[+](1)(35)	High	97 (18)	88 (9)		NA
AKI + RRT					
Sahmeddini(1)(35)	High	0/34	0/33		NA
3-day AKI					
Yassen[+*] (36)	High	80 (18)	97 (18)	80 (27)	NA
5-day AKI					
Mukhtar[+] (37)	High	88 (18)	80 (18)		NA

Observational studies				
Author	RoB	Restrictive group	Liberal group	Calculated OR with 95% CI
1-day AKI				
Lekerika (45)	Critical	16/45	14/44	1.18, 0.49 to 2.85
Wang (41)	Critical	1/25	2/25	0.48, 0.04 to 5.65
Fayed (40)	Moderate	29/45	19/45	2.48, 1.06 to 5.80
Massicotte[+] (42)	Critical	108 (34)	107 (50)	NA
3-day AKI				
Fayed[**] (40)	Moderate	20/45	9/45	3.20, 1.25 to 8.17
Massicotte[***] (42)	Critical	119 (55)	141 (77)	NA
5-day AKI				
Wang (41)	Critical	0/25	1/25	NA
Fayed (40)	Moderate	13/45	4/45	4.16, 1.24 to 14.00
Postoperative AKI				
Choi (44)	Critical	9/44	64/288	0.90, 0.41 to 1.97
Johnson (49)	Critical	6/20	12/20	0.29, 0.08 to 1.06
AKI + RRT				
Lekerika	Critical	1/44	4/44	0.23, 0.02 to 2.12
Fayed (40)	Moderate	3/45	1/45	3.14, 0.31 to 13.42
Schroeder[****] (38)	Critical	5/78	1/73	4.93, 0.56 to 43.26

[+] Mean creatinine concentrations in $\mu mol \cdot L^{-1}$

* This study is a three-arm study. We combined the two more liberal groups together for all analyses

** Reported P value = 0.07

*** Reported P value = 0.001

**** Reported P value < 0.05

AKI = acute kidney injury; CI = confidence intervals; NA = not available; OR = odds ratio; RCT= randomized-controlled trial; RoB = risk of bias; RR = risk ratio; RRT = renal replacement therapy

Means are reported with (standard deviations)

One exposure-based cohort study (restrictive *vs* liberal fluid management) did not show any difference[67] (eTable 3b). Six studies used pulmonary complications as an outcome to categorize the cohort.[58-63] Two studies did not show any difference in the volume received between the groups[59,63] and four reported a higher mean (SD) intraoperative crystalloid volume in the pulmonary complications group [1509 (907) *vs* 1088 (572) mL; $P = 0.03$][58]; total fluid > 100 $mL \cdot kg^{-1}$ in 81% of patients *vs* 58%; $P = 0.014$;[60] total fluid > 10 L in 77% of patients *vs* 52%; $P = 0.008$,[61] and median total fluid of 12.8 L *vs* 8.3–10.3 L in a "late" pulmonary edema group *vs* other groups; $P < 0.05$[62] (eTable 2c).

Duration of MV

We retrieved four RCTs reporting data on the duration of MV (eTable 3c).[33,34,36,37] Pooled results did not show any effect of fluid management on duration of MV (MD, -0.62 days; 95% CI, -3.38 to 2.14; four studies; n = 223; I^2 = 68%)[33,34,36,37] (Fig. 3c). In our first subgroup analysis, intraoperative restrictive fluid management strategies were associated with a shorter duration of MV (MD, -13.04 hr; 95% CI, -22.20 to -3.88; two studies; n = 130; I^2 = 0%)[33,34] (Fig. 3c); this analysis also completely accounted for statistical heterogeneity. In our second subgroup analysis, no effect in either RoB group (high, some concerns) was observed (eFig. 2c). One study used a low-CVP management as their restrictive strategy and suggested an effect (MD, -20.0 hr; 95% CI, -36.8 to -3.2; one study; n = 55).[34]

Four exposure-based (restrictive *vs* liberal fluid management) observational studies reported duration of MV.[40,47,51,67] Two studies did not show any effect of fluid management strategies.[51,67] One study reported a significantly longer duration of MV with a restrictive strategy, not supported by our calculated MD (MD, 1.26; 95% CI, -0.19 to 2.71),[40] and one study reported a shorter median [IQR] duration of MV with a restrictive strategy (20 [16–28] *vs* 94 [49–189] hr; $P < 0.01$)[47] (eTable 3c). Two other studies used MV to categorize their cohort. One study reported that patients with postoperative MV longer than 48 hr did not receive more intraoperative fluid[64] and another study reported that ICU-extubated patients received a lower mean (SD) intraoperative crystalloid volume compared with patients extubated in the operating room [3771 (454) *vs* 5306 (561) mL; $P < 0.05$][65] (eTable 2c).

Other postoperative complications

In the four RCTs[31,34,36,37] and five observational studies[38,39,41,49,67] reporting graft complications (graft failure and acute rejection), fluid management strategy was not associated with these outcomes (eFig. 1a and eTable 3d). Only one perioperative cohort study reported cardiovascular complications (hypotension requiring vasopressors, myocardial infarction, pulmonary embolism, deep vein thrombosis, and postoperative hypertension requiring intravenous antihypertensive agents) but did not show any effect (eTable 3e).[49] Three RCTs[31,36,37] and six observational studies[39,41,46,47,49,67] reported non-pulmonary infection-related complications (reported as either sepsis,[31,41,46,47] infections as a category,[36,37,39,67] or specific site infections)[49]; RCTs did not suggest any effect (eFig. 1b). Only one before-after study suggested a reduced incidence of infection-related complications with restrictive fluid management strategy (16% *vs* 48%) (eTable 3f).[46]

Intraoperative bleeding

Three intraoperative RCTs using a low-CVP target as their restrictive fluid management strategy reported intraoperative bleeding (eTable 3g); pooled data suggested that an intraoperative restrictive fluid management strategy reduced intraoperative bleeding (MD, -1.14 L; 95% CI, -1.72 to -0.57; three studies; n = 226; I^2 = 0%)[31,32,34] (Fig. 3d). When the two studies at high RoB were removed[32,34] the effect was still significant in the study with low RoB (MD, -1.19 L; 95% CI, -1.88 to -0.49; one study; n = 86)[31] (eFig. 2d). Removing the study in which we used median values gave the same results (eFig. 2e).[32]

Five observational studies reported intraoperative bleeding; three of them did not show any effect[39–41] and two studies from the same centre (that included duplicated patients) showed a reduced blood loss with intraoperative phlebotomy[42,43] (eTable 3g). A third study, also originating from the same centre, reported data dichotomized as to bleeding under or over the median from a larger cohort; patients who bled less received less mean (SD) intraoperative crystalloid [3637 (1153) *vs* 4491 (1839) mL; $P < 0.00001$] and were more likely to have had a phlebotomy (65% *vs* 49%; $P < 0.0001$).[66] Part of this cohort was included in previous publications from these authors.[42,43]

Length of stay

Five RCTs reported ICU LOS (eTable 3h); pooled data did not show any association between fluid management and ICU LOS (MD, -0.26 days; 95% CI, -0.92 to 0.41; five studies; n = 311; I^2 = 71%)[31,33,35–37] (Fig. 3e). In our subgroup analyses, we observed a shorter ICU LOS associated with intraoperative restrictive fluid management strategies (MD, -0.79 days; 95% CI, -1.00 to -0.58; three studies; n = 218; I^2 = 0%)[31,33,35] (Fig. 3e) as well as with an intraoperative low-CVP management (MD, -0.8 days; 95% CI, -1.02 to -0.59; two studies; n = 153; I^2 = 0%)[31,35] (eFig. 2h); these subgroup analyses explained the observed statistical heterogeneity. We did not observe a differential effect based on the RoB of the included studies. We also observed no difference in effect when the study reporting medians was removed (eFig. 2f and eFig. 2g).[31] Three RCTs considered hospital LOS; none of them suggested any effect (eFig.1c and eTable 3i).

Nine observational studies reported ICU LOS[38–40,44,47-50,67] and six of them showed no effect.[39,40,44,47,50,67] One intraoperative study suggested

an increased LOS with the use of a restrictive fluid management strategy even though they reported it as non-significant[38] and two intraoperative and postoperative studies suggested a decreased LOS[48,49] with the use of a restrictive fluid management strategy (eTable 3h). Eight studies reported hospital LOS[38,39,42,44,47,67,68]; four did not show any effect,[42,44,47,67] two reported an increased LOS with the use of a restrictive fluid management strategy[38,39] (one of them reported it as non-significant[38] and two suggested a decreased LOS[48,49] with the use of a restrictive fluid management strategy (eTable 3i). Two observational studies reported ICU readmissions and did not show any effect of the fluid management strategy[48,67] (eTable 3j).

Sensitivity analyses for multiple statistical testing

We performed our meta-analyses using larger CIs to adjust for multiple statistical testing (99.4%). The potential protective effects of intraoperative restrictive fluid management strategies on pulmonary complications were no more statistically significant, but significant effects of intraoperative restrictive fluid management strategies were still observed for the duration of MV, intraoperative bleeding, and ICU LOS (eFig. 3).

Summary of findings

We summarized our findings from RCTs in Table 3 (see eTable 4 for the extended version). When considering RoB

TABLE 3 Summary of findings

Outcomes	Nº of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with liberal fluid management	Risk difference with restrictive fluid management
Acute kidney injury (AKI)	86	⊕◯◯◯	**RR 0.88**	19 per 100	**2 fewer per 100**
follow-up: range 1–5 days	(1 RCT)	VERY LOW	(0.35 to 2.20)		(12 fewer to 22 more)
Mortality	118	⊕◯◯◯	**RR 1.08**	21 per 100	**2 more per 100**
assessed with: latest	(2 RCTs)	VERY LOW	(0.54 to 2.15)		(9 fewer to 24 more)
Pulmonary complications (PC)	336	⊕⊕◯◯	**RR 0.78**	36 per 100	**8 fewer per 100**
assessed with: a composite outcome of pulmonary edema, ARDS and pneumonia	(5 RCTs)	LOW	(0.51 to 1.17)		(18 fewer to 6 more)
Duration of mechanical ventilation (MV)	223	⊕⊕◯◯	-		MD **0.62 hours fewer**
	(4 RCTs)	LOW			(3.38 fewer to 2.14 more)
Graft complications	244	⊕◯◯◯	**RR 1.29**	2 per 100	**1 more per 100**
	(4 RCTs)	VERY LOW	(0.27 to 6.17)		(2 fewer to 12 more)
Infection-related complications	179	⊕◯◯◯	**RR 0.60**	11 per 100	**4 fewer per 100**
	(3 RCTs)	VERY LOW	(0.21 to 1.73)		(9 fewer to 8 more)
Bleeding	226	⊕◯◯◯	-		MD **1.14 liters lower**
	(3 RCTs)	VERY LOW			(1.72 lower to 0.57 lower)
Intensive care unit length of stay (ICU LOS)	311	⊕◯◯◯	-		MD **0.26 days fewer**
	(5 RCTs)	VERY LOW			(0.92 fewer to 0.41 more)
Hospital length of stay (hospital LOS)	191	⊕⊕◯◯	-		MD **0.93 fewer**
	(3 RCTs)	LOW			(2.57 fewer to 0.7 more)

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

CI = confidence interval; ICU = intensive care unit; MD = mean difference; RCT = randomized-controlled trial; RR = risk ratio

across studies, imprecision, and indirectness (as defined in the GRADE methodology) the overall quality of evidence was either low or very low.[30]

Discussion

Our work summarized evidence on perioperative fluid management strategies in adult liver transplant recipients. Based on a low or very low quality of evidence from RCTs, fluid management strategies did not seem to have any effect on the risk of AKI or mortality. Intraoperative restrictive fluid management strategies might be associated with fewer pulmonary complications, reduced duration of MV, lower intraoperative blood loss and a reduced ICU LOS. Limited data on other important outcomes, such as graft, cardiovascular, and infection-related complications, were reported. Even though the subgroup analyses of this review suggest that an *intraoperative restrictive fluid management strategy* might have a protective effect on some of these complications, the level of certainty is insufficient to support any recommendation.[21,22,69]

The majority of RCTs' restrictive protocols were intraoperative low-CVP management protocols based on restricted fluid administration and were associated with most of the observed effects. Further insight into different types of fluid management protocols was provided by data gathered from observational studies. Most of these studies compared either CVP-oriented management with usual care or retrospectively classified groups, and suggested that pulmonary complications and bleeding might be reduced by a restrictive fluid management strategy. Although the two RCTs that reported no effect on AKI used an intraoperative low-CVP management,[31,35] one of the two observational studies at moderate RoB compared low-CVP management with goal-directed therapy and suggested an increased risk of AKI with low-CVP management.[40] This effect might be explained by a temporal improvement effect, but a real harmful effect of low-CVP management or a real protective effect of goal-directed therapy might also be possible. Central venous pressure is a poor predictor of fluid responsiveness[70] and low CVP-based fluid management protocols probably do not achieve the same benefits as other goal-directed strategies, such as stroke volume optimization.[17] We found one small (n = 53) postoperative RCT at high RoB[36] and five observational studies that used a stroke volume based goal-directed therapy in at least one group,[40,41,44,47,51] which provided insufficient evidence to draw firm conclusion on these strategies.

In many other surgical populations, there is good evidence to support a protective effect of goal-directed fluid management strategies that limit and tailor volume administration to physiological parameters, such as stroke volume, while fixed restrictive fluid management protocols might increase AKI.[14,17,18,71] Liver transplant recipients may have concomitant cardiorespiratory comorbidities, which may require specific fluid management strategies. Goal-directed fluid strategies tailored to the various surgical phases might be more effective than a fixed fluid management strategy. The effects of such goal-directed protocols in this population should be further explored.

Levels of CVP have been directly correlated with portal hypertension and bleeding in liver transplant recipients,[66,72,73] which concurs with the association of reduced blood loss with intraoperative low-CVP management protocols that we observed.[31,32,34] This benefit was particularly robust in the subgroup and sensitivity analyses. The addition of a phlebotomy to an overall low-CVP strategy was described in one centre.[42,43,66] Phlebotomy was consistently associated with lower blood loss and, even though this study had residual and uncontrolled confounding, was the only intervention associated with a lower mortality in the two studies with moderate RoB.[43]

Many cohort studies conducted in this population suggested an association between perioperative variables, such as hypotension, vasopressor dose, or number of transfusions and postoperative complications, such as mortality, AKI, graft failure, and pulmonary and infection-related complications.[6-9] In our study, we observed potential effects of fluid management on important postoperative outcomes that should be further explored. Observational cohort studies suggested an association between hypotension and the need for high doses of vasopressors and increased postoperative complications. The potentially confounding effects of vasopressor requirement and fluid management strategies on outcome merits further research in this population.

This review has some limitations. The major limitation is the small number of RCTs and the overall limited quality of evidence. Most RCTs (five out of seven) had a high RoB and most of the observed effects were from these studies. Although we identified many observational studies, most of them had either a high or critical RoB, and were before-after studies that did not adjust for temporal effects; these did not improve our level of certainty. We included all types of protocols and perioperative periods, with inherent clinical diversity and between-studies variability. Results came mostly from intraoperative studies, and so there is limited information regarding postoperative interventions. Differential effects associated with various fluid management protocols or periods of intervention (intraoperative *vs* postoperative) on any outcome had to be obtained from several subgroup meta-analyses; the multiple statistical testing could indicate a "significant" effect simply by chance alone. Nonetheless, most of our

findings were statistically significant using a very conservative adjustment for multiple statistical testing on secondary outcomes. Statistical heterogeneity was also explained by our subgroup analyses and our results were consistent across outcomes, strengthening the robustness of our findings. The main strength of this review is the thorough evaluation of the currently available evidence by a very systematic approach that limits the chances of missing any important study reporting at least one clinically significant postoperative outcome. Another strength is that we assessed the RoB with two novel tools recommended by the Cochrane Collaboration.

Clinical equipoise on the best fluid management strategy to adopt in this population still remains and high-quality data are needed to improve perioperative quality of care in these patients. Outcomes such as intraoperative bleeding, duration of MV, ICU LOS, and pulmonary complications seemed to be improved by a restrictive fluid management strategy and should be included in future research outcome studies. We strongly suggest that hemodynamic goals be integrated into any future RCT concerned with a fluid management protocol in liver transplant recipients.

Based on low or very low levels of evidence, we did not observe any association between restrictive fluid management strategies and AKI. Nevertheless, intraoperative restrictive fluid management strategies might have protective effects on other clinical outcomes, such as blood loss, duration of MV, ICU LOS, and pulmonary complications. This review will help to guide the design of future clinical trials concerned with the optimal perioperative fluid management strategy for patients undergoing liver transplantation.

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Alexis F. Turgeon and *Marc Bilodeau* contributed to study conception and design; analysis and interpretation of data; and drafting the article. *Han Ting Wang*, *Pierre Aslanian*, and *Stéfanie Iorio* contributed to acquisition, analysis and interpretation of data and drafting the article.

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Protocol amendments We removed postoperative red blood cell and procoagulant blood product transfusions from our outcomes.

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