The safety of restrictive fluid therapy for major abdominal surgery: a systematic review and meta-analysis

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Abstract

Background: Restrictive fluid therapy is essential to enhanced recovery after surgery. A meta-analysis was conducted to explore the safety of restrictive fluid therapy for major abdominal surgery and compare it with liberal fluid therapy.

Methodology : We searched MEDLINE, the Cochrane Central Register of Controlled Trials for randomized controlled trials (RCTs), the WHO International Clinical Trials Registry Platform, and EMBASE in which restrictive and liberal fluid therapies were compared. Data on complications, anastomotic leaks, and wound infections were extracted.

Results: Eleven RCTs comparing the two therapies were included. Compared with liberal fluid therapy, restrictive fluid therapy lowered the risk of complications and cardiopulmonary dysfunction and had similar rates of mortality, anastomotic leak, pneumonia and would infection. But increased kidney injury was also observed in restrictive fluid therapy.

Conclusion: Restrictive fluid therapy is safe but may have potential dangers, so caution is warranted in its application.

Background

Enhanced recovery after surgery (ERAS) has been a research focus. ERAS was first put forward by Kehlet, a Danish surgeon, who intended to reduce complications, relieve the patient's stress, and shorten hospital stay after abdominal surgery [1]. Restricting fluids, as a component of ERAS, is designed to accelerate the patient's recovery after a major surgery [2].

Preoperative fluid management includes two strategies: (1) liberal fluid therapy using unmonitored fixed regimens and estimated fluid loss (high[3–4] or low[5–8] volume of fluid); (2) restrictive fluid therapy based on the maximized flow-related parameters[9–10]. Fluid overload causes tissue edema, which thereby can lead to impaired oxygenation and anastomotic breakdown [5, 11 –14]. Liberal fluid therapy may cause abdominal-compartment syndrome, a postoperative or post-traumatic increase of intra-abdominal pressure, which exerts adverse physiologic impacts, including respiratory insufficiency, kidney failure, pancreas edema, intestinal intolerance, extended intestinal paralysis, sepsis and multiorgan failure caused by translocation of bacteria and endotoxin into the blood[23]. However, excessive fluid restriction may lead to hypovolemia and hypoperfusion in the tissue [15–16]. Tissue hypoperfusion caused by insufficient fluid regimen, inflammation, reperfusion injury, ischemia, and sepsis impairs vascular integrity [17–18]. Consequently, fluid loss accompanied by gradual redistribution of interstitial, intracellular, and intravascular space, results in dehydration and then may lead to acute hypovolemia (including endocrine–metabolic stress activation, cardiopulmonary dysfunction, and sleep disruption) [19–20]. Due to increased fluid in intestines, gastrointestinal edema and dysfunction may occur [21–22]. Nevertheless, maintaining adequate intravascular fluid is crucial for normal organ perfusion. Inappropriate intravascular fluid intervention is strongly associated with postoperative complications after major abdominal surgery[24–30]. However, the safety of fluid in the perioperative period of abdominal surgery remains unclear[31–34].

Some papers based on subgroup analysis have demonstrated that restrictive fluid therapy and liberal conventional therapy have similar incidences of overall and cardiopulmonary complications [35]. A more recent study has shown that compared with liberal fluid regimen one year after surgery, restrictive fluid regimen leads to a higher rate of acute kidney injury[36]. Therefore, the safety of restrictive fluid therapy is highly disputed. The objective of this meta-analysis was to assess and compare the safety of restrictive fluid therapy and liberal fluid therapy in terms of complication rate, anastomotic leak, wound infection, kidney injury, and cardiopulmonary dysfunction. We also aimed to explore the limitations, and strengths of restrictive fluid therapy.

Methods

Search strategy

We searched the following databases: the Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform, EMBASE, and MEDLINE for relevant studies from 2000 to present. Keywords searched were "fluid therapy," "restrictive", "restriction" and "abdominal surgery." The latest search was conducted on July 1, 2019. The studies were limited to RCTs with follow-ups about 15 days but with no information of age, sex, and weight. A manual search of the reference lists were conducted to retrieve the related articles. Another manual search was conducted using search engines to retrieve relevant abstracts from international meetings.

Inclusion And Exclusion Criteria

Inclusion criteria: (1) Restrictive fluid replacement (1.0L to 2.7L) vs. liberal fluid regimens(2.8L to 5.4L)[68] ;(2) Adult patient with detailed information; (3) RCTs; (4) Major abdominal surgery with or without stoma; (5)American Society of Anesthesiologists grade I-III (without life-threatening systemic diseases); (6)Assessment for patients who received liberal or restrictive fluid therapy during surgery. Comparison of preoperative fluid therapies (including one restricted fluid therapy and one conservative or liberal fluid volume therapy) must be included.

Exclusion criteria: (1) Articles with no full text or non-comparative studies; (2) Disseminated or secondary tumor, diabetes, inflammatory bowel disease, renal deficiency (serum creatinine level > 180 μmol/l), alcohol overconsumption, mental disorders, pregnancy, lactation, and contraindications of epidural analgesia; (3) Case reports

Data Collection And Data Analysis

Study selection

Full-length articles and abstracts of RCTs involving restrictive fluid therapy for major abdominal surgery with liberal fluid therapy as control were included. Letters, animal studies, reviews, or case reports were excluded.

Data Extraction

The quality of methodology and relevance to this meta-analysis of the included studies were evaluated. This meta-analysis was conducted according to the QUOROM statement. Two authors extracted and compared data on complications and readmission of each study independently[84].

Assessment Of Risk Of Bias

Following the Cochrane Collaboration's bias framework[37], we identified the following bias for each study: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias) (patient-reported outcomes); (5) Blinding of outcome assessment (detection bias) (Mortality); (6) Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2–6 weeks)) (7) Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (> 6 weeks)) (8) Selective reporting (reporting bias). Each bias was graded as low risk, unclear risk, or high risk, which was used to evaluate the overall bias risk in each study. The Cochrane Collaboration's recommendation was used to determine whether the bias across domains could lead to date bias and predict the possible bias [37].

Statistical analysis

Statistical analysis was performed application Review Manager software version 5.0.0 Complications (anastomotic leaks, wound infection, kidney injury, cardiopulmonary, pneumonia, and mortality) were evaluated using pooled odds ratio (OR) with 95% confidence intervals (CIs) [84]. χ2 tests assess statistical heterogeneity, and statistical significance was set as $P < 0.1$. The I^2 statistic evaluates the impact of heterogeneity. When the heterogeneity test indicated statistically significance, the random-effects model was applied. Two-sided P□0.05 were considered statistically significant. The publication bias was assessed using Funnel plots and the Egger's test[84].

Results

Search results

Among the 472 articles selected from the databases, based on abstract reading, 272 articles were excluded according to the criteria in Fig. 1. After reading the complete text, among the 78 remaining articles, excluded were 15 articles with no relevant data about the outcome of restrictive fluid therapy for major abdominal surgery, 54 that were not RCTs, 2 that were meta-analyses, and 7 that were from the same trial. Finally, 11 RCTs published between 2000 and 2018 that compared restrictive fluid therapy with liberal fluid therapy were

included. Two studies[36], [48] by the same team were taken as one trial and shared the same study number because some data from the two studies were complementary.

Characteristics Of The RCTS

The characteristics of the 11 studies[36][38–47] are presented in Table 1. As shown in Table 2, the included studies had a low bias. Among the 4030 patients, 2018 were given restrictive fluid therapy and 2012 were given liberal fluid therapy.

Table 1
Main characteristics of the 11 included studies

			N		Age (years)		Sex (M:F)	
	Years	Way	R	L	R	L	R	L
Myles[36]	2018	Abdominal	1490	1493	66 ± 13	66 ± 13	771/719	783/710
Futier[39]	2010	Abdominal	36	34	61.9 ± 12	60.4 ± 14	20/16	19/15
Cohn[41]	2010	colorectal	18	9	56.1 ± 10	45.9 ± 15	8/10	6/3
Nordling[42]	2011	colorectal	79	82	68	69	43/36	45/37
Piljic[43]	2015	Abdominal	30	30	68.64 ± 7	69.34 ± 8	22/8	26/8
Weinberg[44]	2017	pancreas	26	26	61	68	15/11	14/12
Srinivasa[45]	2012	colorectal	37	37	72 ± 12	69 ± 16	22/15	19/18
Phan[40]	2014	colorectal	50	50	65 ± 19	63 ± 23	31/19	30/20
Challand[46]	2012	colorectal	89	90	66 ± 15	65.9 ± 14	54/35	48/42
Brandstrup[47]	2012	colorectal	79	71	68.1 ± 14.9	66.9 ± 14.9	47/32	28/43
Peng[38]	2013	Abdominal	84	90	62	63	45/39	49/41
R = restrictive fluid therapy ; L = liberal fluid therapy; M = male; F = female								

Table 2

Risk-of-bias assessment of the randomized controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2–6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (> 6 weeks))	Selective reporting (reporting bias)
Myles[36]	Low	Low	Low	Low	Low	Low	Low	Low
Futier[39]	Low	Unclear	Low	Low	Low	Low	Low	Low
Cohn[41]	Low	Low	Low	Unclear	Low	Low	Low	Low
Nordling[42]	Low	Low	Low	Low	Low	Low	Low	Low
Piljic[43]	Low	Low	Low	Low	Unclear	Low	Low	Low
Weinberg[44]	Unclear	Low	Low	Low	Low	Unclear	Low	Low
Srinivasa[45]	Low	Low	Low	Low	Unclear	Low	Low	Low
Phan[40]	Low	Low	Unclear	Low	Low	Low	Low	Low
Challand[46]	Low	Low	Low	Low	Unclear	Low	Unclear	Low
Brandstrup[47]	Low	Low	Low	Low	Unclear	Low	Low	Low
Peng[38]	Unclear	Low	Low	Low	Low	Low	Low	Low

Selection bias is based on random sequence generation and allocation concealment; performance bias includes blinding of participants and study investigators for the outcomes of interest; detection bias includes blinding of outcome assessors; attrition bias indicates systematic loss of participants in one arm, which could lead to missing outcome data for that trial arm over the other trial arm; and reporting bias includes the possibility of selective outcome reporting. Selection bias is a feature of the trial design. Performance and detection bias are overall low given that most data were collected without any prior knowledge of the investigators of the tested hypothesis in this study at the time of event collection. All analysis in this report are based on intention-to-treat and we further mitigated the possible effect of any attrition bias and reporting bias at individual trial level by collection of additional unpublished data.

Meta-analysis Results

Compared with liberal fluid therapy, restrictive fluid therapy reduced the risk of complications. The pooled OR was 1 (95% CI: 0.88–1.14; P = 0.99; Fig. 2 and Table 3), χ^2 was 112.07 (P < 0.0001), and I^2 was 51%.

Table 3
OR and 95% CI of complications for restrictive fluid therapy with liberal fluid therapy during major abdominal surgery in all of the patients.

				heterogeneity	
Outcome or Subgroup	Studies	Participants	Effect Estimate	I^2(%)	P-value
Restrictive vs Liberal					
Patients with complications	6	560	0.84 [0.60, 1.18]	59	0.31
Mortality	6	3542	1.55 [0.92, 2.60]	0	0.10
Cardiopulmonary	10	3851	0.66 [0.48, 0.91]	52	0.01
kidney injury	8	3679	1.76 [1.35, 2.29]	0	0.0001
Anastomotic leak	5	432	1.13 [0.58, 2.20]	57	0.73
Wound Infection	8	694	1.26 [0.80, 2.01]	0	0.32
Pneumonia	8	3603	0.99 [0.70, 1.40]	0	0.94
Total complications	8	798	0.54 [0.39, 0.75]	78	0.0003

Patients With Complications

Six studies (including 560 patients) presented data on complications; 45.8% (132/288) patients in the restrictive fluid therapy group had complications compared with 50% (136/272) patients in the liberal fluid therapy group. Pooling of results demonstrated that patients who received restrictive fluid therapy had a significantly lower rate of complications than those who received liberal fluid therapy. The WMD was 0.86 (95% CI: 0.60–1.18; P = 0.31), χ^2 was 12.22 (P = 0.003) and I^2 was 59%, which excluded the heterogeneity among the studies.

Mortality

Six studies (including 3542 patients) presented data on mortality: the mortality in the restrictive fluid therapy group was 2.0% (36/1774) and 1.3% (23/1768) in the liberal fluid therapy group. Pooling of results suggested that restrictive fluid therapy did not decrease mortality compared with liberal fluid therapy. The WMD was 1.55 (95% CI: 0.92–2.60; P = 0.10), χ^2 was 1.67 (P = 0.89), and I^2 was 0%, which excluded the heterogeneity among the studies.

Cardiopulmonary Dysfunction

Ten studies (including 3851 patients) presented data on cardiopulmonary dysfunction: 3.9% (75/1929) patients in the restrictive fluid therapy group had cardiopulmonary dysfunction compared with 5.6% (107/1922) in the liberal fluid therapy group. Pooling of results indicated that restrictive fluid therapy significantly reduced cardiopulmonary dysfunction compared with liberal fluid therapy. The WMD was 0.66 (95% CI: 0.48–0.9; P = 0.01), χ^2 was 18.87 (P = 0.03), and I^2 was 52%, indicating the heterogeneity among the studies.

Kidney Injury

Eight studies (including 3679 patients) presented data on kidney injury: 8.6% (158/1837) patients had kidney injury in the restrictive fluid therapy group and 5.1% (94/1832) in the liberal fluid therapy group. Pooling of results suggested that restrictive fluid therapy did not decrease kidney injury compared with liberal fluid therapy. The WMD was 1.76 (95% CI: 1.35–2.29; P < 0.0001), χ^2 was 3.82 (P = 0.70), and I^2 was 0%, indicating that the liberal fluid therapy group had a significantly lower rate of kidney injury than the restrictive fluid therapy group.

Anastomotic Leak

Five studies (including 432 patients) provided data on anastomotic leak: 9.1% (20/220) patients in the restrictive fluid therapy group had an anastomotic leak compared with 8.0% (17/212) in the liberal fluid therapy group. Pooling of results indicated that restrictive fluid therapy did not decrease anastomotic leak compared with liberal fluid therapy. The WMD was 1.13 (95% CI: 0.58–2.20; P = 0.73), χ^2 was 9.31 (P = 0.05), and I^2 was 57%, which excluded the heterogeneity among the studies.

Wound Infection

Eight studies (including 694 patients) presented data on wound infection: 13.5% (48/355) patients in the restrictive fluid therapy group had wound infection while 10.6% (36/339) in the liberal fluid therapy group had it. Pooling of results indicated that restrictive fluid therapy did not decrease wound infection compared with liberal fluid therapy. The WMD was 1.26 (95% CI: 0.80–2.0; P = 0.32), χ^2 was 5.85 (P = 0.56), and I^2 was 0%, which excluded the heterogeneity among the studies.

Pneumonia

Eight studies (including 3603 patients) presented data on pneumonia: 3.5% (63/1808) patients in the restrictive fluid therapy group had pneumonia while 3.5% (63/1795) patients in the liberal fluid therapy group had it. Pooling of results indicated that restrictive fluid therapy did not decrease pneumonia compared with liberal fluid therapy. The WMD was 0.99 (95% CI: 0.70–1.40; P = 0.94), χ^2 was 4.48 (P = 0.72), and I^2 was 0%, which excluded the heterogeneity among the studies.

Total Complications

Eight studies (including 798 patients) presented data on total complications: 61.5% (248/403) patients in the restrictive fluid therapy group had total complications while it was 84.8% (335/395) in the liberal fluid therapy group. The WMD was 0.54 (95% CI: 0.39–0.75; P = 0.0003), χ^2 was 22.68 (P = 0.0004), and I^2 was 78%. Pooling of results indicated that restrictive fluid therapy significantly decreased total complications compared with the liberal fluid therapy.

Publication Bias

The funnel plot was used to assess the overall bias of inclusion literature. The shapes of the funnel plots did not demonstrate obvious asymmetry (Fig. 3).

Discussion

The present meta-analysis demonstrated that compared with liberal fluid therapy, restrictive fluid therapy had a lower risk of complications and cardiopulmonary dysfunction and a similar potential of mortality, anastomotic leaks, wound infection, and pneumonia; however, increased kidney injury was observed in the restrictive fluid therapy group. The safety of restrictive fluid therapy after major abdominal surgery is of great concern globally.

Perioperative intravenous-fluid therapy is used to maintain homeostasis via restoring body fluid, electrolytes, and organ perfusion. ERAS recommends that excessive intravenous fluid should be avoided[49–53]. Some trials have supported restrictive fluid therapy[54–56]. However, the harm caused by inappropriate fluid balance interventions cannot be neglected[57–58]. In particular, inadequate fluid intervention may lead to acute kidney injury [59]. Hypoglycemia-induced tissue hypoxia may cause postoperative complications. A recent study has shown that fluid restriction can reduce intestinal microcirculatory blood flow and tissue-oxygen tension[60]. Some researchers have observed that fluid restriction can decrease preoperative $ScvO_2$, which is associated with hypovolemia and postoperative complications. Other studies have demonstrated that $ScvO_2$ changes indicate circulatory disturbances during tissue hypoxia[61–63]. By monitoring oxygen extraction, Donati found early correction of altered tissue oxygenation reduces postoperative complications[64]. However, liberal fluid therapy after major abdominal surgery increases the risk of postoperative complications. The occurrence of

complications can be attributed to the extravascular accumulation of fluids caused by systematic inflammatory response, elevated microvascular permeability of large amounts of intravenous solution and prepared blood products, and hemodynamic-anesthesia.

Intravenous-fluid intervention after abdominal surgery is classified as restrictive (< 1.75L/day), balanced (1.75–2.75L/day)[65], and liberal (> 2.75L/day). The patients in restrictive fluid group received a median of 1.7L fluid during surgery and another 1.9L in the first 24 hours after surgery. The patients in the liberal fluid group received 3.0L intraoperatively and an another 3.0L in the first 24hours after surgery (similar to the amount recorded in registry data24 and pooled analyses of trials)[66–67]. In the previous studies, intraoperative restrictive fluid replacement ranged 1.0L-2.7L compared with 2.8L-5.4L in the liberal fluid therapy[68]. A recommended weight gain of < 2.5 kg[69–70] was achieved in a majority of the patients, including those in the liberal fluid group.

Several RCTs have shown better outcomes in patients upon esophageal Doppler-guided fluid optimization. Esophageal Doppler monitoring can effectively [71–74] detect hypovolemia and predict volume responsiveness [75–76]. Hypovolemia has been proved as an independent predictor of anastomotic leak and postoperative sepsis. Hypovolemia can result in poor organ perfusion and thus cause organ dysfunction[77–78]. Because of the high incidence of tissue hypoperfusion in major abdominal surgery[79–80], it is essential to detect and correct occult hypovolemia early and use the early-warning tissue-hypoperfusion signals.

All the four systematic reviews reporting results of meta-analyses on this topic[34–35, 81, 82] have concluded that compared with liberal fluid therapy, restrictive fluid therapy can reduce complications and should be advised as the preferred fluid-management policy.

The present meta-analysis is the first to compare restrictive fluid therapy with liberal fluid therapy for major abdominal surgery. We demonstrated that restrictive fluid therapy had reduced rates of complications and cardiopulmonary dysfunction and similar potentials of mortality, anastomotic leak, wound infection, and pneumonia. However, increased kidney injury is observed in patients who received restrictive fluid therapy. This paper is also the first to propose that restrictive fluid therapy for major abdominal surgery should be used with caution. Evidence come from included studies, in which all the risks of bias for the outcomes of interest were low (Table 2).

Several limitations exist in this paper. First, the mount of sample was small in some studies. The authors and journals or institutions of publication were not blind to data extraction and analyses; yet two researchers performed literature selection and data extraction independently, so selection risk was unlikely. Second, the asymmetry in the funnel plots for some results indicated reporting bias. However, clinical and statistical heterogeneity may also lead to the asymmetric funnel. Finally, qualities of life after surgery, which are important factors for patients, were not taken into account in the included studies[84].

Conclusion

To conclude, the current meta-analysis assessed the effects of restrictive fluid therapy in a meticulous way. Though the large proportional reduction in risk of complications as indicated in the previous literature was not confirmed, moderate but clinically notable reduction in complications is still worth our attention. The application of restrictive fluid therapy requires communication and cooperation between medical workers and patients. RCTs on restrictive fluid therapy with long-term follow-up are needed. Hospital costs and quality of life after surgery should also be taken into account. Furthermore, the benefits of restrictive fluid therapy in elderly patients and patients who have undergone other surgeries might be the focus of future research.

Abbreviations

enhanced recovery after surgery (ERAS); randomized controlled trials(RCTs)

Declarations

- Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

- Consent to publish All patients allow publishing.

- Availability of data and materials All authors approve to share the dates of paper.

- Competing interests The authors declare that they have no competing interests

- Funding No

- Authors' ContributionsSW, DG and ZT contributed equally to this study; SW and DG designed the review, ZT and YZ provided supervision. CM and PL identified and acquired reports of trials, abstracted data and assessed risk of bias. All of the authors approved the final version of the manuscript submitted for publication and are guarantors for the study.

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Figures

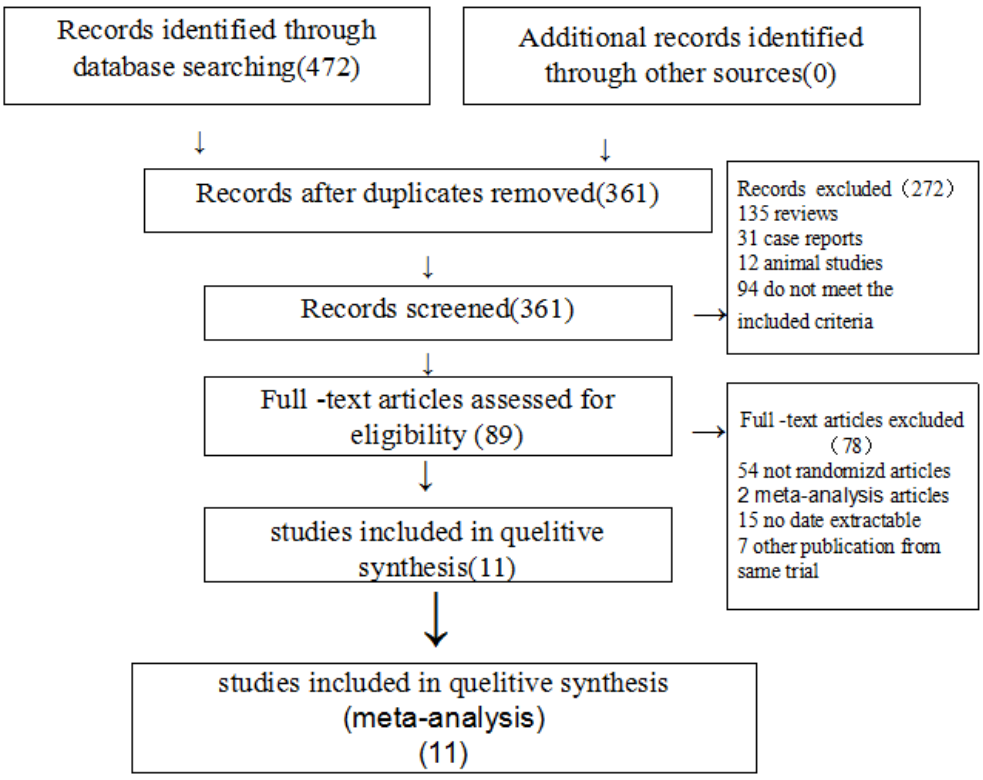

Figure 1

Selection of studies.

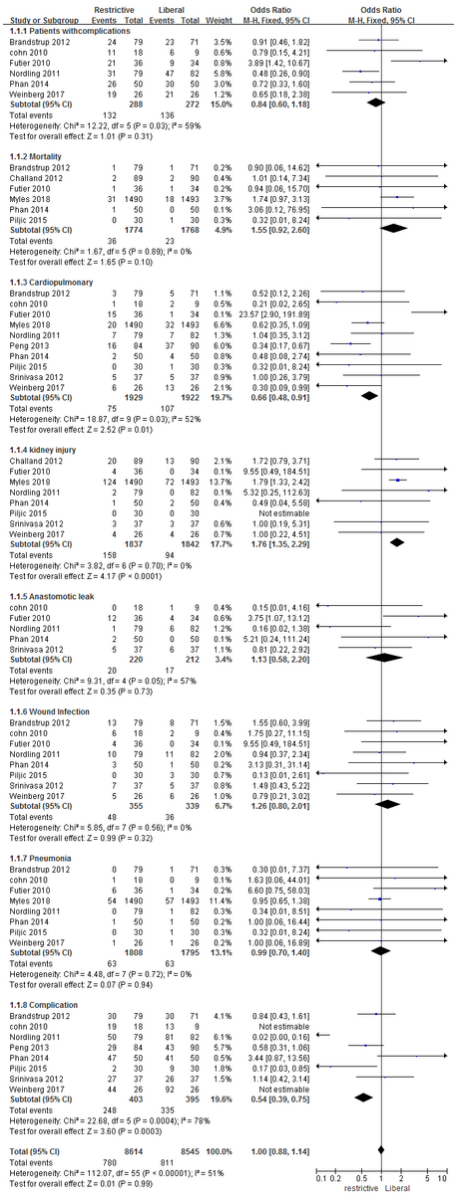

Figure 2

Forest plot of comparison: Complications.Odds ratios are shown with 95% CIs.

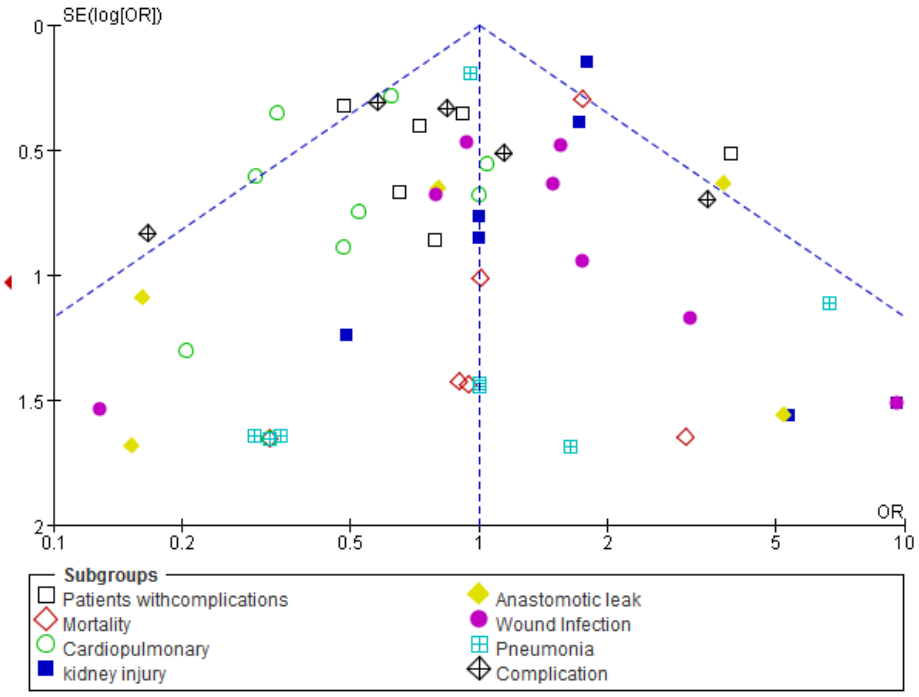

Figure 3

Forest plot of comparison: Complications.OR, odds ratio.

Supplementary Files

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