Liberal Versus Restricted Fluid Resuscitation Strategies in Trauma Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Observational Studies*

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Objective: Hemorrhage is responsible for most deaths that occur during the first few hours after trauma. Animal models of trauma have shown that restricting fluid administration can reduce the risk of death; however, studies in patients are difficult to conduct due to logistical and ethical problems. To maximize the value of the existing evidence, we performed a meta-analysis to compare liberal versus restricted fluid resuscitation strategies in trauma patients.

Data Sources: Medline and Embase were systemically searched from inception to February 2013.

Study Selection: We selected randomized controlled trials and observational studies that compared different fluid administration strategies in trauma patients. There were no restrictions for language, population, or publication year.

Data Extraction: Four randomized controlled trials and seven observational studies were identified from 1,106 references. One of the randomized controlled trials suffered from a high protocol violation rate and was excluded from the final analysis.

Data Synthesis: The quantitative synthesis indicated that liberal fluid resuscitation strategies might be associated with higher mortality than restricted fluid strategies, both in randomized controlled trials (risk ratio, 1.25; 95% CI, 1.01–1.55; three trials; I^2, 0) and observational studies (odds ratio, 1.14; 95% CI, 1.01–1.28; seven studies; I^2, 21.4%). When only adjusted odds ratios were pooled for observational studies, odds for mortality with liberal fluid resuscitation strategies increased (odds ratio, 1.19; 95% CI, 1.02–1.38; six studies; I^2, 26.3%).

Conclusions: Current evidence indicates that initial liberal fluid resuscitation strategies may be associated with higher mortality in injured patients. However, available studies are subject to a high risk of selection bias and clinical heterogeneity. This result should be interpreted with great caution. (*Crit Care Med* 2014; 42:954–961)

Key Words: fluid therapy; meta-analysis; resuscitation; shock; time factors; trauma

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Dr. Lee had full access to all data and has final responsibility to submit the results for publication.

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Multiple trauma is the major cause of mortality and disability in children and young adults worldwide, with 5 million deaths occurring in 1990; this is expected to increase to 8 million deaths per year by 2020 (1). The two leading causes of mortality in trauma are neurological injury and blood loss (2, 3). Hemorrhage is responsible for approximately 80% of trauma deaths within the first few hours and 65% of such deaths in hospital (4).

For patients with major trauma, defined as having an injury severity score (ISS) of more than or equal to 16 (5), advanced trauma life support guidelines currently advocate "balanced" resuscitation with initial 1–2 L of crystalloids before definitive surgical control of bleeding (6). The animal models showing a survival benefit from aggressive fluid therapy were almost exclusively investigated in the setting of "controlled hemorrhage," that is, volume resuscitation began after definite hemostasis was achieved in animal models of hemorrhagic shock (7, 8). The applicability of these studies to real trauma patients is questionable because most trauma patients experience "uncontrolled hemorrhage," in which traumatic wounds remain unrepaired when volume resuscitation begins.

Interest in models of resuscitation of uncontrolled hemorrhage emerged in the late 1980s and early 1990s. Several animal studies have shown a reduced risk of death using a lower-than-normal blood pressure as a guide to fluid resuscitation in a strategy referred to as hypotensive resuscitation (9–11). A recent review of fluid resuscitation strategies in animal models revealed a consistent improvement in mortality with employment of this approach (12). Aggressive fluid resuscitation might cause increased bleeding from dislodged clots (13). Furthermore, aggressive resuscitation might also result in dilutional coagulopathy, which may worsen bleeding (14, 15).

Unfortunately, most studies of uncontrolled hemorrhage have been conducted in animals, and clinical studies often pose logistical and ethical difficulties. To maximize the clinical value of the existing evidence, this meta-analysis quantitatively pooled the results of randomized controlled trials (RCTs) and observational studies to compare the effect of liberal and restricted fluid resuscitation strategies on outcomes in patients with trauma-related hemorrhage.

MATERIALS AND METHODS

Data Sources and Searches

We performed this meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines (16) and the Meta-analysis Of Observational Studies in Epidemiology guidelines (17). We performed searches for literature related to fluid resuscitation in trauma patients on the Medline and Embase databases from their inception through to February 2013. We did not set restrictions on publication date, country, or language. The search terms for the primary intervention included hypotensive resuscitation, small/limited/restricted volume resuscitation, and delayed resuscitation. The search results were then crossed-checked for the population of interest and searched using the terms of trauma, hemorrhagic shock, hypovolemic shock, and shock. In addition, we checked the reference lists of relevant review articles. Selection of pertinent studies was performed independently by two reviewers. Discrepancies between the reviewers were resolved by a consensus meeting with the third or fourth coauthor.

Study Selection

To be eligible for inclusion, studies had to 1) compare liberal versus restricted fluid administration and include mortality as an outcome; 2) include trauma patients; and 3) use an RCT or observational study design. Cohort studies, and case-control studies with an appropriate control group, were eligible. IV fluids included crystalloid solutions, colloids, and blood products. We excluded studies comparing different types of fluid, such as IV administration of crystalloids versus colloids. Studies with more than 10% burn patients in the cohorts were excluded.

Data Extraction and Quality Assessment

Data were extracted for study location, number of participants, setting (prehospital or in-hospital), population characteristics (mean age and gender composition), major trauma mechanism (blunt or penetrating), mean ISS, type of resuscitation strategy used in the experimental and comparison groups, outcome, and crude and adjusted effect sizes and corresponding CIs. Mortality was specified as the primary outcome of the present review.

The Cochrane Risk of Bias Tool was adopted to assess the risk of bias for each RCT (18). Observational studies were evaluated using the Newcastle-Ottawa Scale (19, 20).

We attempted to contact the authors to procure the missing data. When the adjusted effect sizes were not available, manual calculations of unadjusted effect estimates (odds ratio [OR]) were performed for inclusion in our meta-analysis. Otherwise, such analyses were excluded.

Data Synthesis and Analysis

Data were analyzed separately for RCTs and observational studies. For RCTs, data were combined and expressed as Mantel-Haenszel weighted average of the risk ratios (RRs) with their associated 95% CIs. For observational studies, ORs were the primary effect measure for weighted summary estimates. Most observational studies used restricted fluid strategy as the reference group in regression analysis. For convenience, we designated liberal and restricted fluid strategies as the exposure and control groups, respectively. If a study provided multiple comparisons with the same control group, we selected the appropriate comparison groups to fulfill the hypothesis of hypotensive resuscitation by two a priori set rules: 1) the maximum volume difference between comparison groups and 2) the minimum fluid volume in the control group.

In both analyses, heterogeneity was measured by the Cochran Q statistic ($p < 0.05$) and quantified with the I^2 statistic (21, 22). Fixed-effects models were used when the I^2 value was less than 50%, and random-effects models were used when the I^2 value was more than 50% (23). To explore the source of heterogeneity, we defined potential relevant covariates a priori and tested them one at a time in the meta-regression model. We re-estimated effect sizes stratified on the same covariates, so that they were available as separate estimates in subgroup analysis. The presence and the effect of publication bias were examined by Begg and Egger tests. The metan, metabias, heterogi, and metareg macros were performed using Stata 11.0

(StataCorp, College Station, TX). The *p* values of less than 0.05 were considered statistically significant.

RESULTS

Search Results and Study Characteristics

In the systemic review, we identified 11 studies, including four RCTs (24–27) and seven observational studies (28–34) (**Fig. 1**; **supplemental data**, Supplemental Digital Content 1, http://links.lww.com/CCM/A790)

RCTs. The four RCTs (24–27) included 2,107 patients between the years of 1994 and 2011. The mean age ranged from 31 to 43 years and the proportion of men ranged from 64% to 94%. The locations of resuscitation differed among the included trials. The mean prehospital time in the two trials with emergency medical services (EMS) was 29 minutes (24) and 57 minutes (25), respectively. The proportions of penetrating and blunt injuries also differed in included trials. Except for the trial by Turner et al (25), the other three trials excluded patients with traumatic brain injury (TBI) and enrolled patients with major trauma (mean ISS ≥ 16). Only Turner et al (25) explicitly excluded patients with burn injury. Most trials except the one by Turner et al (25) required blood pressure less than 90 mm Hg for enrollment. A restricted fluid strategy was achieved by delaying fluid resuscitation until arrival at hospital in two prehospital trials (24, 25) or using a lower-than-normal blood pressure as a guide for fluid resuscitation in two in-hospital trials (26, 27).

Observational Studies. The seven observational studies (28–34), including three case-control studies (29, 30, 33) and four retrospective cohort studies (28, 31, 32, 34), encompassed 13,687 patients between the years 1990 and 2012. The mean ages and proportions of men were similar in the observational studies and RCTs. Five studies were conducted in prehospital settings (28–31, 33). The mean prehospital time ranged from 28 to 74 minutes. However, in contrast to the RCTs, the observational studies involved more patients with blunt injury and TBI. All observational studies did not explicitly exclude patients with burn injury. Most studies included patients with a mean ISS of more than or equal to 16. Most studies required patients with systolic blood pressure less than 90 mm Hg for inclusion or controlled blood pressure as a confounding factor in regression analysis except two studies (28, 29). Four studies compared prehospital resuscitation with and without fluid administration (28–31); three studies compared the effect of different volumes of fluid administration (32–34). Four studies (29–32) did not provided mean volume infused in comparison groups: one study (30) compared fluid resuscitation more than 500 mL with no fluid resuscitation and two trials (31, 32) controlled fluid volume as a confounding factor in regression analysis. Three studies (31, 32, 34) used crystalloids only in resuscitation; one study (33) used both crystalloids and colloids; and the remaining three studies (28–30) did not report which type of fluid was used. Except for the study by Kaweski et al (28), all other studies used matching or regression analysis to control for confounding factors, such as age, gender, ISS, and blood pressure. In five studies performed in the EMS setting, only the studies by Sampalis et al (29) and Talving et al (31) controlled for prehospital time as a confounding factor.

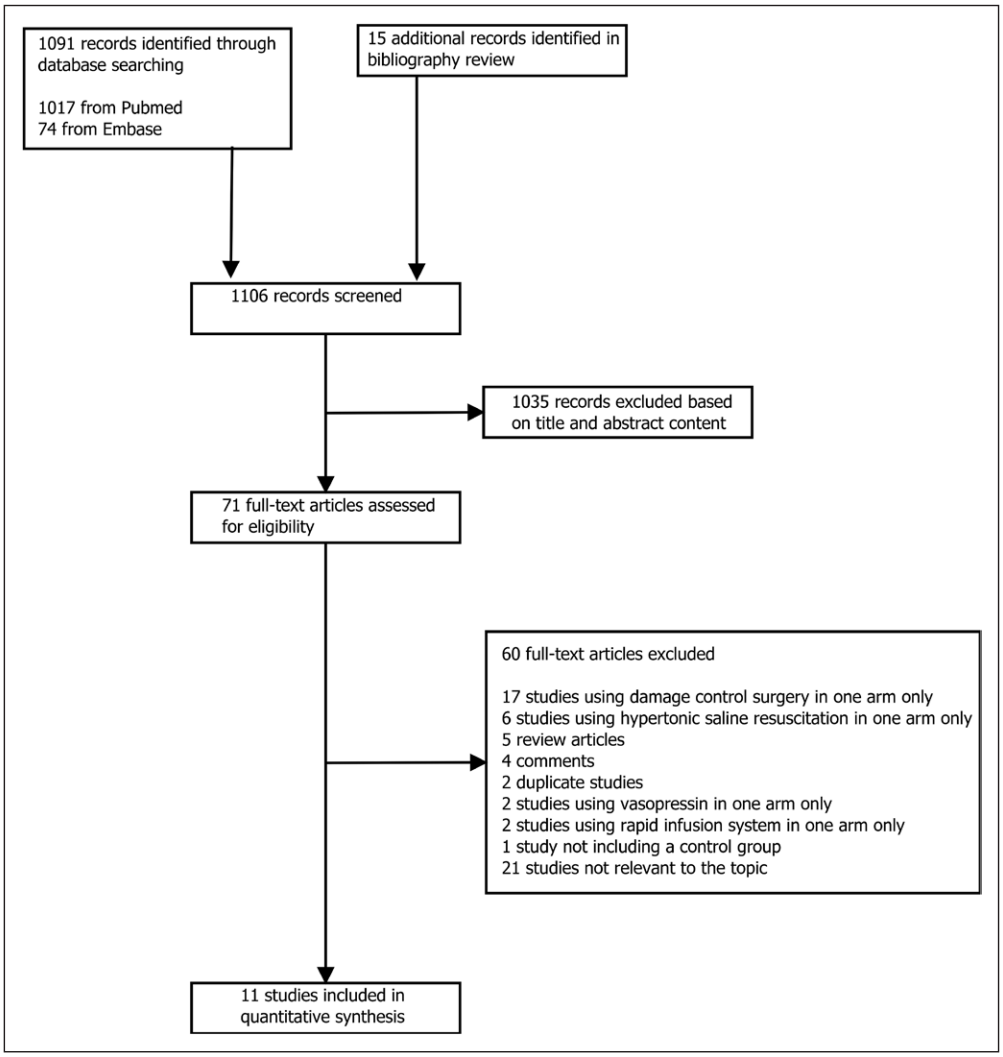

Figure 1. Literature search flow diagram.

Quality Assessment. Of the four RCTs, two trials (26, 27)

TABLE 1. Assessment of Risk of Bias for Randomized Controlled Trials

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting
Bickell et al (24)	High	High	High	Low	Unclear
Turner et al (25)	High	High	High	Low	Low
Dutton et al (26)	Unclear	Unclear	High	Low	Unclear
Morrison et al (27)	Unclear	Unclear	High	Low	Unclear

did not clearly report the random sequence generation or allocation concealment (Table 1). Bickell et al (24) randomized patients by alternate day allocation without sequence concealment. Turner et al (25) randomized paramedics rather than patients using a computer-generated sequence. Blinding processes were not used in all trials. All data were managed by intention-to-treat analysis. Among observational studies, only the study by Kaweski et al (28) failed to establish comparability between the two comparison groups; otherwise, all observational studies achieved similar scores on the Newcastle-Ottawa Scale. Notably, the protocol violation rate was high in the RCT by Turner et al (25), resulting in similar proportions of patients receiving fluid administration in the two comparison groups.

Across all studies, mortality was recorded at different time points. For the purpose of meta-analysis, overall mortality was specified as death within the longest follow-up period available for each study. This included death in hospital (24, 26, 30, 32, 33); death within 7 days (29), 30 days (27, 31), and 6 months (25); and death during an unspecified period (28, 34). Twenty-four-hour mortality, reported by two RCTs (26, 27), was also synthesized. All of 24-hour mortalities were caused by exsanguination (26, 27).

Quantitative Data Synthesis

RCTs. For the four RCTs, there was no significant difference in overall mortality between liberal and restricted fluid resuscitation strategies (RR, *1.*18; 95% CI, 0.98–1.41; I^2, 0%) (**Fig. 2*A***). After excluding the trial by Turner et al (25), which included a drastically different study population and a high protocol violation rate, the summary estimates showed that the liberal fluid resuscitation strategy was associated with significantly higher overall mortality (RR, 1.25; 95% CI, 1.01–1.55; I^2, 0%) (**Fig. 2*B***). Twenty-four-hour mortality was not significantly different between two strategies (RR, 1.29; 95% CI, 0.58–2.88; I^2, 0%; two studies).

Observational Studies. Among the observational studies, the study by Ley et al (32) provided effect estimates on two independent cohorts with different age ranges, both of which were included in this analysis. Talving et al (31) stratified the liberal resuscitation group into three levels (1–500 mL of crystalloids, > 500 mL of crystalloid, and hypertonic saline/dextran 250 ± crystalloids) in the regression analysis; Ley et al (32) used four cutoff points (1, 1.5, 2, and 3 L) to distinguish between liberal and restricted fluid resuscitation. To avoid multiple comparisons, the exposure group with more than 500 mL of crystalloids in the trial by Talving et al (31) and cutoff point of 1 L in the trial by Lety et al (32) were selected for analysis by a priori set rules.

The summary estimate showed that liberal fluid resuscitation was associated with significantly higher mortality in patients with trauma-related hemorrhage conditions (OR, 1.14; 95% CI, 1.01–1.28; I^2, 21.4%) (**Fig. 3*A***). The strength of this harmful effect increased (OR, 1.19; 95% CI, 1.02–1.38; I^2, 26.3%) when we restricted analysis to adjusted studies (**Fig. 3*B***; **Table 2**).

Most subgroup analyses did not reveal significant differences between the two strategies (Table 2). Likewise, in meta-regression, the effect estimates were not significantly changed by these characteristics. Begg and Egger tests did not indicate significant publication bias.

DISCUSSION

The present review identified four RCTs and seven observational studies exploring the effect of two fluid administration strategies on mortality in trauma patients. Our analysis showed that a liberal fluid resuscitation strategy, as compared with a restricted fluid resuscitation strategy, was associated with higher overall mortality in patients with trauma-related hemorrhage, both in RCTs (RR, 1.25; 95% CI, 1.01–1.55; I^2, 0%) and observational studies (OR, 1.14; 95% CI, 1.01–1.28; I^2, 21.4%). However, this result should be interpreted with caution.

For RCTs, Turner et al (25) adopted different inclusion and exclusion criteria. In contrast to the other three RCTs, the trial by Turner et al (25) enrolled more patients with blunt injuries or TBI and more patients with low ISS. Furthermore, their study has been criticized for its high protocol violation rate (35), resulting in randomization failure. These two reasons justified the exclusion of the trial by Turner et al (25) from quantitative data synthesis.

The studies by Dutton et al (26) and Morrison et al (27) set different blood pressure goals for the liberal and restricted fluid resuscitation groups. However, probably because of the spontaneous cardiovascular compensation mechanism in the early stage of trauma-hemorrhage, these two trials could not generate significant pressure differences between the experimental and control groups. In the trial by Morrison et al (27), there was no significant difference for the amount of fluid infused, either. This could partly explain the null effect of the restricted fluid resuscitation strategies in the trials by Dutton et al (26) and Morrison et al (27).

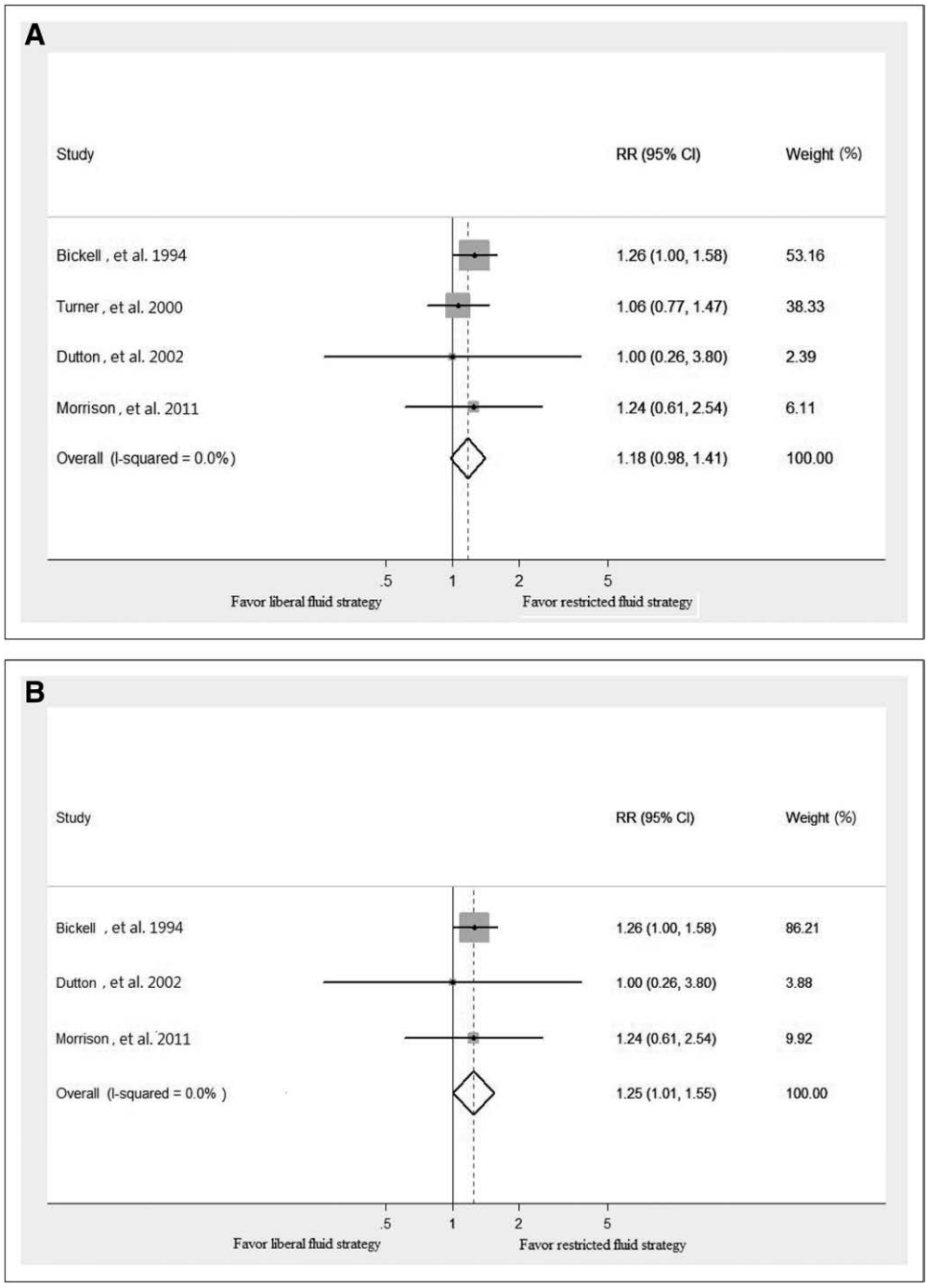

Figure 2. A, Forest plot for randomized controlled trials. Comparison of the effects of liberal versus restricted fluid resuscitation on overall mortality, expressed as risk ratio (RR) and 95% CI. **B**, Forest plot for randomized controlled trials after exclusion of the trial by Turner et al (25). Comparison of the effects of liberal versus restricted fluid resuscitation on overall mortality, expressed as RR and 95% CI.

Only the trial by Bickell et al (24), in which fluid administration was delayed until patient arrival at the operating room, established differences in the amount of fluid received by the two comparison groups; the trial also showed a significant difference in mortality between the two strategies. Because of its large sample size, the final pooled result was predominantly determined by the trial by Bickell et al (24) (weight: 86.21%). It has to be noted that the short prehospital transportation time in the trial by Bickell et al (24) might limit the generalizability of this trial's results to other prehospital settings where longer prehospital transportation time is needed.

One of the main differences between the study populations in the RCTs and observational studies was the types of injury. There were more patients with blunt injury and TBI in the observational studies, whereas most RCTs included patients with penetrating injury and excluded patients with TBI. Animal studies have mainly been conducted in hemorrhagic shock induced by vascular penetrating injury (12). Blunt injury is a more complicated mechanism. Furthermore, in the presence of TBI, the potential benefits of permissive hypotension might be compromised by the consequence of cerebral hypoperfusion (36).

Observational studies were highly subject to selection bias and confounding by indication. Adjusting confounding factors using statistical methods to generate comparability between exposure and control groups was highly recommended (37). Most observational studies in the current review provided ORs adjusted by important confounding factors, including age, ISS, and blood pressure at the scene. However, most of these studies did not account for prehospital time or elapsed time before definite surgical repair. The benefits of the "scoop and run" versus prehospital stabilization strategies in areas with predictably short transport times had been debated (38). Without adjustment for prehospital time or elapsed time before definite surgical repair, it would be difficult to determine whether the observed mortality was caused by the liberal fluid resuscitation strategy or prolonged transport time.

Locations of resuscitation in current analysis included prehospital and in-hospital settings. The experience of rescuers and resources involved in resuscitation differed significantly in these settings. The result of meta-regression in observational

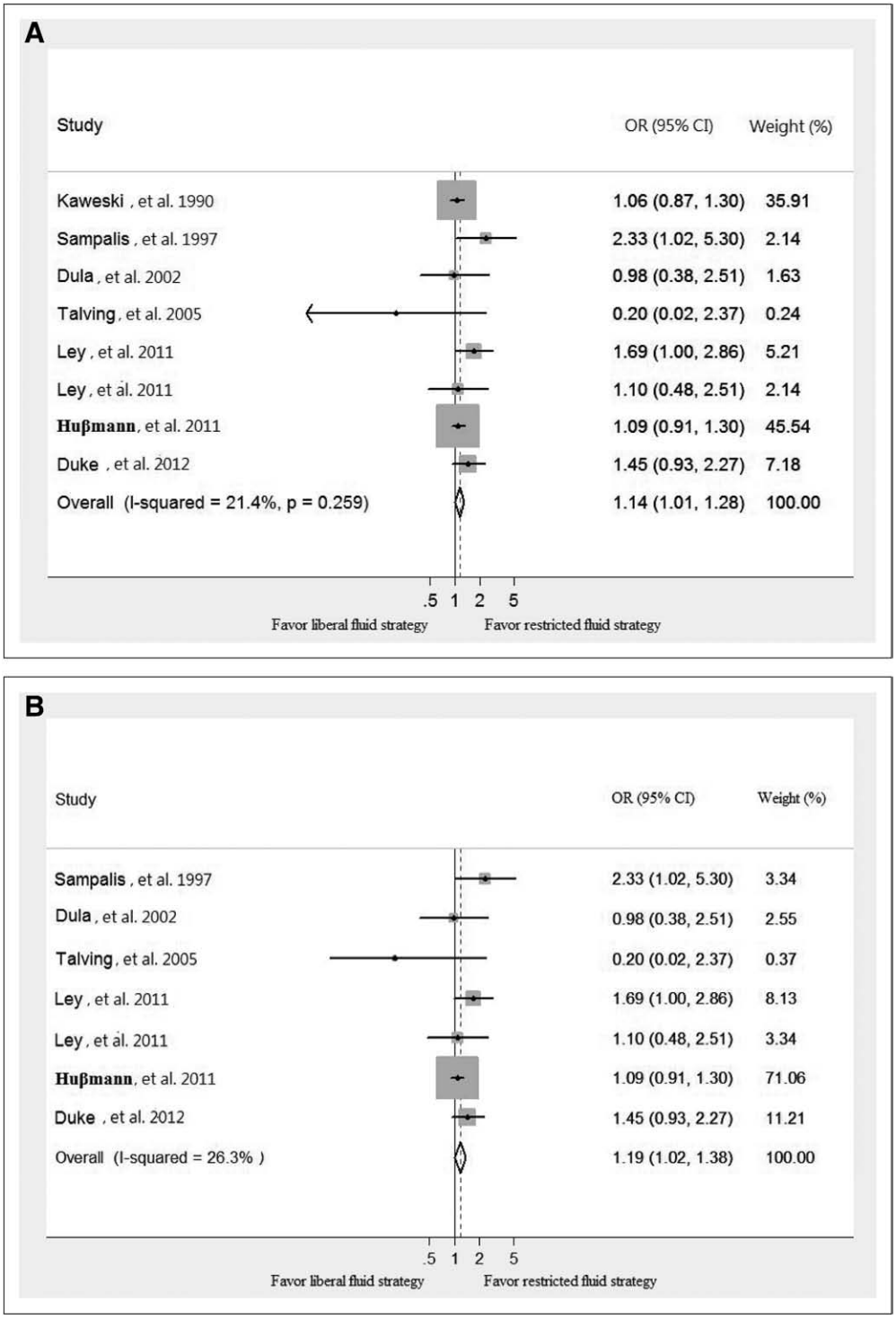

Figure 3. A, Forest plot for observational studies. Comparison of liberal versus restricted fluid resuscitation on overall mortality, expressed as odds ratio (OR) and 95% CI. **B**, Forest plot for observational studies with adjusted OR. Comparison of liberal versus restricted fluid resuscitation on overall mortality, expressed as OR and 95% CI.

studies did not demonstrate significant differences between prehospital and in-hospital settings. However, because of the limited number of studies included in analysis, type II error and other uncontrolled confounding factors might cause this null difference.

Two studies performed in the EMS settings excluded patients who did not survive to hospital from the 7-day (29) and 30-day (31) mortality analyses, respectively. This might introduce selection bias, because it is unknown whether there was a difference in mortality before hospital arrival between the two strategies. For those who survived to hospital, the use of either restricted or liberal fluid administration might not have significantly influenced outcome. However, rapid fluid resuscitation might be beneficial for patients with severe circulatory compromise before hospital arrival in some conditions, such as tension pneumothorax or cardiac tamponade (39). Therefore, patients who collapse during transport before arrival at hospital should be included in such analyses to make this treatment recommendation more applicable (although those with no pulse at the scene should remain excluded).

Hemorrhage accounts for most cases of early mortality in trauma patients, while organ failure accounts for most cases of late mortality (4). In current analysis, liberal fluid resuscitation did not result in more 24-hour mortalities, all of which were caused by exsanguination. However, only two RCTs reported 24-hour mortality, which was subject to type II error. The causes of late mortality were usually multifactorial. Therefore, only overall mortality was reported.

LIMITATIONS

First, most studies were performed in prehospital settings. The generalizability of our result to other settings, such as emergency department or operating room, should be further examined. Second, patients with burn injury needed a unique strategy for fluid resuscitation. Restricted fluid resuscitation might not be applied to these patients. Finally, the primary purpose of the present meta-analysis is not to recommend a specific method of restricted fluid resuscitation but rather to determine whether the concept of restricted fluid resuscitation

TABLE 2. Subgroup Analysis of Observational Studies

Subgroup Analysis	Included Studies	Odds Ratio (95% CI)	I^2 (%)	*p* for Meta-Regression
Studies with adjusted odds ratios	(29–34)	1.19 (1.02–1.38)	26.3	0.63
Without fluid resuscitation in restricted fluid group	(28–31)	1.09 (0.90–1.32)	42.5	0.572
With fluid resuscitation in restricted fluid group	(32–34)	1.17 (1.00–1.37)	11.0	0.580
Male predominance (> 70%)	(28–34)	1.14 (1.01–1.29)	31.9	0.880
Age > 40 yr	(29, 30, 32, 33)	1.16 (0.99–1.37)	24.9	0.608
Injury severity score ≥ 16	(28, 30, 31, 33, 34)	1.10 (0.97–1.24)	0	0.106
Study with emergency medical service	(28–31, 33)	1.09 (0.96–1.24)	23.3	0.130
Study with crystalloids only for resuscitation	(31, 32, 34)	1.42 (1.01–1.97)	6.7	0.234

would affect survival based on currently available evidence. Future investigators are encouraged to compare the relative efficacy and safety of different restricted fluid resuscitation strategies in an adequately powered RCT.

CONCLUSIONS

The pooled results from the RCTs suggest that a restricted fluid strategy might be useful in trauma patients with penetrating injury but without TBI. On the basis of the pooled results from the observational studies, the use of restricted fluid resuscitation strategies could be expanded to include those with blunt injury or TBI. Given the inherent limitations of observational studies, this conclusion should be interpreted cautiously, and further confirmation in prospective RCTs is needed.

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