Effect of goal-directed fluid therapy on renal function in critically ill patients: a systematic review and meta-analysis

Cong-Cong Zhao, Yan Ye, Zhi-Qiang Li, Xin-Hui Wu, Chai Zhao, Zhen-Jie Hu

Department of Intensive Care Unit, The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; Department of Intensive Care Unit, North China University of Science and Technology Affiliated Hospital, Tangshan, China

ABSTRACT

Objective: To evaluate whether goal-directed fluid therapy (GDFT) reduces the risk of renal injury in critical illness.

Methods: MEDLINE via PubMed, EMBASE, CENTRAL and CBM was searched from inception to 13 March 2022, for studies comparing the effect of GDFT with usual care on renal function in critically ill patients. GDFT was defined as a protocolized intervention based on hemodynamic and/or oxygen delivery parameters. A fixed or random effects model was applied to calculate the pooled odds ratio (OR) based on heterogeneity through the included studies.

Results: A total of 28 studies with 9,019 patients were included. The pooled data showed that compared with usual care, GDFT reduced the incidence of acute kidney injury (AKI) in critical illness (OR 0.62, 95% confidence interval (CI) 0.47 to 0.80, \(p < 0.001\)). Sensitivity analysis with only low risk of bias studies showed the same result. Subgroup analyses found that GDFT was associated with a lower AKI incidence in both postoperative and medical patients. The reduction was significant in GDFT aimed at dynamic indicators. However, no significant difference was found between groups in RRT support (OR 0.88, 95% CI 0.74 to 1.05, \(p = 0.17\)). GDFT tended to increase fluid administration within the first 6 h, decrease fluid administration after 24 h, and was associated with more vasopressor requirements.

Conclusions: This meta-analysis suggests that GDFT aimed at dynamic indicators may be an effective way to prevent AKI in critical illness. This may indicate a benefit from early adequate fluid resuscitation and the combined effect of vasopressors.

ARTICLE HISTORY
Received 5 January 2022
Revised 23 March 2022
Accepted 24 April 2022

KEYWORDS
Acute kidney injury; fluid therapy; critical care; systematic review; meta-analysis

Introduction

Acute kidney injury (AKI) is a clinical syndrome due to an abrupt decrease in kidney function and is typically diagnosed by increased creatinine, decreased urine output, or both [1]. It is a common and serious complication in critically ill patients and is associated with increases in hospitalization cost, morbidity, and mortality [2,3]. It should be noted that just with the occurrence of AKI, short- and long-term survival will be significantly reduced for patients with AKI regardless of its severity and evolution [4]. Therefore, the prevention of AKI is crucial in critically ill patients.

AKI prevention is a multimodal clinical algorithm based on protocolized volume status and perfusion pressure optimization [5], which require adequate renal blood flow. Unfortunately, routine hemodynamic measurements, such as the mean blood pressure (MAP) and central venous pressure (CVP), are poor predictors of volume status and renal blood flow in critical illness. The end points of fluid resuscitation are uncertain and challenging, which leads to the development of protocolized hemodynamic resuscitation. This goal-directed fluid therapy (GDFT) approach uses intensive monitoring, including some measures of hemodynamics (such as MAP, CVP, cardiac output (CO), and stroke volume (SV)) and oxygen delivery parameters (such as oxygen delivery, central venous oxygenation (ScvO2) or mixed venous oxygenation).

GDFT reduced the risk of perioperative complications [6,7], including renal injury [8]. A recent meta-analysis found that GDFT improved renal perfusion and oxygenation in high-risk patients undergoing major abdominal
and orthopedic surgery [9]. In addition, previous studies have suggested that GDFT is associated with a decrease in AKI incidence in critical illness [10–12]. However, some studies found no beneficial effect of GDFT on renal function [13–15]. Furthermore, different kinds of patients, protocolized goals, and study designs make it difficult to provide specific recommendations for GDFT.

Hence, this meta-analysis aimed to evaluate the effects of GDFT on renal function in critically ill patients. In particular, we tried to clarify which protocolized goals are effective, what kinds of patients can benefit from them, and the roles of fluids and vasopressors in this approach.

Methods

Protocol and registration

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [16]. The protocol of this work was registered in the PROSPERO database (CRD42021233518).

Search strategy

We searched the MEDLINE via PubMed, EMBASE, CENTRAL and CBM databases (from inception to 13 March 2022) using the terms: (“intensive care” or “emergency” or “critical illness”) AND (“fluid resuscitation” or “fluid therapy”) AND (“goal-directed” or “goal-oriented” or “target-directed”). There were no language limits on eligibility. The Supplementary Material 1 shows the search strategy in more detail.

Study selection

Two investigators (CCZ, YY) independently determined whether eligible studies met the following PICOS criteria: 1) Population: adult patients (age ≥18 years) treated at an intensive care unit or emergency department; 2) Intervention: protocolized and based on hemodynamic and oxygen delivery parameters; 3) Control: usual care, defined as conventional treatments that were at the discretion of the clinicians. Monitoring by CVP or MAP measurements was allowed. 4) Outcomes: The primary outcome was the incidence of AKI at any time point during hospitalization, whichever definition of AKI was adopted. Secondary outcomes were renal replacement therapy (RRT) support, fluid administration, and vasopressor requirements. 5) Type of studies: randomized controlled trials (RCTs), quasi-RCTs, and prospective and retrospective controlled trials.

The exclusion criteria were as follows: 1) lack of a protocolized intervention; 2) lack of a baseline condition or control group; 3) lack of data on any renal outcome: AKI and RRT; and 4) no original studies, case reports, case series, animal studies, in vitro studies, and studies without full text.

Data extraction

The initial and full-text reviews and data extraction from the included studies were performed independently by two authors (CCZ, YY). The kappa coefficient was calculated as a measure of agreement about study selection and quality appraisal. Any discrepancies were resolved by the third author (ZQL), and a decision was reached by consensus.

Data were collected using a predesigned form. For each study, the following information was extracted: publication (last name of the first author, year of publication), participant characteristics (including patient source, diagnosis, demographic data, clinical setting, and number of patients), targets used in the GDFT protocol (including MAP, CVP, CO/CI, SV, stroke volume variation (SVV), pulse pressure variation (PPV), oxygen delivery parameters et al.), study design, and outcome data.

Assessment of risk of bias

Two authors (CCZ, YY) independently assessed the risk of bias to evaluate the quality of the included studies. The Cochrane Collaboration tool [17] was used for RCTs, and the ROBINS-I tool (Risk of Bias in Nonrandomized Studies of Interventions) [18] was used for non-RCTs. Funnel plot was used to evaluate publication bias.

Statistical analysis

SPSS 25.0 was used to calculate the kappa coefficient. Data analysis was conducted using RevMan 5.3. The results are presented as forest plots using odds ratios (ORs) for dichotomous data and the mean difference (MD) for continuous data. All estimates were provided with 95% confidence intervals (CIs). Heterogeneity was assessed by Cochran’s Q statistic and the I² test. A P value >0.1 or I² statistic below 50% indicated low levels of heterogeneity. In these cases, a fixed-effect model was used. Otherwise, a random-effects model (Mantel-Haenszel method) was selected. Sensitivity analysis with only low risk of bias studies was considered if the pooled data of the primary outcome had
significant heterogeneity. Several subgroup analyses were performed for the primary outcome according to population (postoperative and medical patients), GDFT protocol (early goal-directed therapy (EGDT) [11], dynamic indicators (defined as the variation of certain indicators in the GDFT protocol), and other protocols), and the design of the trial (RCT and non-RCT). $p < 0.05$ indicated statistical significance.

**Results**

The search strategy identified 1,768 unique publications, and 2 additional records were identified from reference lists. After excluding duplicates ($n = 258$) and screening titles and abstracts ($n = 1,512$), 111 studies were assessed in full text for eligibility (Figure 1). Following full-text review, a total of 28 studies met the inclusion criteria (kappa = 0.858, $p < 0.01$). Among these, three studies were reported in Chinese [19–21], and all the other studies were reported in English [10,14,22–44].

The characteristics of the included studies are summarized in Table 1. In total, the included studies comprised 9,019 patients, and the number of patients per study was 48 to 1,591. Of the 28 included studies, 21 studies were RCTs, and the other seven were not. The risk of bias assessments for RCTs and non-RCTs are shown in Figure 2 (kappa = 0.766, $p < 0.01$). The green, red and yellow colors indicate a low risk of bias, a high risk of bias, and an unclear risk of bias, respectively. Studies with more than or equal to five green plus were considered low risk of bias studies. Among the 28 included studies, all except for five studies [27,28,38,40,42] had a low risk of bias overall.
| Studies                  | Country                | Design                  | Department                | Population | No. of patients (GDFT vs. Control) | GDFT proposal | Control          | Outcomes                  |
|-------------------------|------------------------|-------------------------|---------------------------|------------|-----------------------------------|---------------|-------------------|----------------------------|
| McKendry et al. 2004    | United Kingdom         | RCT                     | Surgical ICU              | post-surgery | 174 (89 vs. 85)                   | SVI > 35 ml/m² & increase ≤ 10% after fluid challenge | usual care | AKI, fluids administration |
| Lin et al. 2006         | China                  | RCT                     | Medical ICU               | septic shock | 224 (108 vs. 116)                | EGDT without SvO₂ | usual care | AKI, fluids administration, vasopressor requirement |
| Jhanji et al. 2010      | United Kingdom         | RCT                     | ICU                       | post-surgery | 90 (45 vs. 45)                    | SV increase < 10% after fluid challenge | CVP rise ≥ 2 mmHg | AKI, fluids administration |
| Goepfert et al. 2013    | Germany                | RCT                     | ICU                       | post-surgery | 92 (46 vs. 46)                    | SVV ≤ 10%     | CVP > 8 or MAP > 65 mmHg | AKI, fluids administration |
| Kanji et al. 2014       | Canada                 | prospective before-after study | ICU                       | undifferentiated shock | 220 (110 vs. 110) | IVC collapsibility < 15% | usual care | AKI, fluids administration, vasopressor requirement |
| Peake et al. 2014       | Australia & New Zealand | RCT                     | Emergency department      | early septic shock | 1591 (793 vs. 798) | EGDT | usual care | RRT, fluids administration, vasopressor requirement |
| Pearson et al. 2014     | United Kingdom         | RCT                     | ICU                       | post-surgery | 734 (368 vs. 366)                | CO-guided hemodynamic therapy algorithm | usual care | AKI, fluids administration |
| Pestaña et al. 2014     | Spain                  | RCT                     | ICU                       | post-surgery | 142 (72 vs. 70)                   | MAP ≥ 65 mmHg & CI ≥ 2.5 L/min/m² | usual care | AKI, fluids administration |
| Suzuki et al. 2014      | Australia              | prospective before-after study | ICU                       | post-surgery | 98 (53 vs. 45)                    | CVP 8 – 12 mmHg | usual care | AKI, fluids administration |
| Thomson et al. 2014     | United Kingdom         | prospective cohort study | Cardiothoracic ICU        | post-surgery | 264 (123 vs. 141)                | SV increase < 10% after fluid challenge | standard therapy | AKI, RRT, fluids administration |
| Yealy et al. 2014       | United States          | RCT                     | Emergency department      | septic shock | 895 (439 vs. 456)                | EGDT | usual care | AKI, RRT, fluids administration |
| Mouncey et al. 2015     | United Kingdom         | RCT                     | Emergency department      | early septic shock | 1251 (625 vs. 626) | EGDT | usual care | RRT, fluids administration, vasopressor requirement |
| Liu et al. 2016         | China                  | prospective before-after study | ICU                       | Moderate brain injury & traumatic shock | 98 (48 vs. 50) | EGDT | usual care | AKI, fluids administration |
| Jin et al. 2016         | China                  | retrospective before-after study | ICU                       | post-surgery | 232 (131 vs. 101)                | CVP 10 – 12 mmHg; CI ≥ 2.4 L/min/m²; lactate ≤ 2.4 mmol/L; SvO₂ ≥ 65% | MAP 65-100 mmHg | AKI, fluids administration |
| Schmid et al. 2016      | Germany                | RCT                     | ICU                       | post-surgery | 180 (92 vs. 88)                   | MAP > 70 mmHg, CI > 2.5 L/min/m²; GEDI > 800 mL/m²; ELWI < 10 ml/kg | usual care | AKI, RRT, fluids administration |
| Latham et al. 2017      | United States          | retrospective cohort study | Medical or Transplant ICUs | post-surgery | 191 (100 vs. 91)                  | SVI increased < 10% after fluid challenge | usual care | RRT |
| Luo et al. 2017         | China                  | RCT                     | ICU                       | severe sepsis & septic shock | 145 (73 vs. 72) | CVP > 8 or MAP > 65 mmHg | usual care | AKI, fluids administration |
| Yu et al. 2017          | China                  | RCT                     | ICU                       | COPD with septic shock | 71 (34 vs. 37) | GEDI > 800 mL/m² | usual care | AKI, fluids administration |
| Huang et al. 2018       | China                  | RCT                     | ICU                       | hypovolemic shock | 48 (25 vs. 23) | EGDT | CVP 8 – 12 mmHg | AKI, fluids administration |
| MacDonad et al. 2019    | United Kingdom         | RCT                     | ICU                       | post-surgery | 287 (144 vs. 143)                | CO-guided hemodynamic therapy algorithm | usual care | AKI, fluids administration, vasopressor requirement |
| Pan et al. 2019         | China                  | RCT                     | ICU                       | post-surgery | 171 (103 vs. 68)                  |                | usual care | AKI, RRT |

(continued)
| Studies                          | Country                        | Design                  | Department                  | Population       | No. of patients (GDFT vs. Control) | GDFT proposal                                                                                   | Control | Outcomes |
|--------------------------------|--------------------------------|-------------------------|-----------------------------|-----------------|-----------------------------------|------------------------------------------------------------------------------------------------|
| Douglas et al. 2020 [23]       | United States & United Kingdom | RCT                     | Emergency department & ICU  | sepsis or septic shock | 150 (102 vs 48)                 | CI > 2.5 L/min/m²; GEDVI > 700 mL/m² or ITBVI > 850 mL/m²; EVLWI < 10 mL/kg; MAP > 65 mmHg     | usual care | RRT     |
| Martin et al. 2020 [31]        | United Kingdom                 | RCT                     | ICU                         | post-surgery septic shock | 60 (30 vs. 30)                  | SVV ≤ 10% (non-MV) or ITBVI distensibility < 18% (MV)                                       | usual care | RRT     |
| Musikatavorn et al. 2021 [34]  | Thailand                       | RCT                     | Emergency department        | Septic shock      | 220 (101 vs. 101)                 | CI > 2.5 L/min/m², SVV < 13%                                                                | usual care | RRT, fluids administration, vasopressor requirement |
| Parke et al. 2021 [35]         | Australian & New Zealand       | RCT                     | Surgical ICU                | post-surgery      | 715 (358 vs. 357)                 | CI > 2.5 L/min/m², SVV < 13%                                                                | usual care | RRT, fluids administration, vasopressor requirement |
| Waal et al. 2021 [42]          | China                          | RCT                     | Surgical ICU                | post-surgery      | 482 (234 vs. 248)                 | age-dependent target for CI & SVV and PLR                                                  | usual care | AKI     |
| Wang et al. 2021 [43]          | Netherlands                    | RCT                     | PACU / ICU                  | post-surgery      | 134 (66 vs. 68)                   | Bioelectrical impedance analysis                                                           | usual care | AKI, fluids administration |
| Froghi et al. 2022 [44]        | United Kingdom                 | RCT                     | ICU                         | post-surgery      | 60 (30 vs. 30)                    | SV rise ≤ 10%, SV drop ≤ 10%                                                               | usual care | AKI     |

AKI: acute kidney injury; CO: cardiac output; CI: cardiac index; COPD: chronic obstructive pulmonary disease; CVP: central venous pressure; EGDT: early goal directed therapy; EVLWI extravascular lung water index; ICU: intensive care unit; ITBVI: Inferior Vena Cava; GDFI: Global end-diastolic index; MAP: mean blood pressure; MV: mechanical ventilation; No.: number; PACU: Post-Anesthesia Care units; PLR: passive leg raising; PV: pulse pressure variation; RCT: randomized controlled trial; RRT: renal replacement therapy; ScvO2: central venous oxygenation; SvO2: mixed venous oxygenation; SV: stroke volume; SVI: stroke volume index.
Incidence of AKI

Twenty-two \((n = 5,649, 2,853\) in the GDFT group and \(2,796\) in the control group) of the 28 included studies reported that the incidence of AKI ranged from 0\%–95\% with different follow-up times. All but six of the included studies reported a clear definition of AKI. The incidence of AKI was lower in postoperative patients and higher in medical patients. The detailed parameters of AKI, including the morbidity, definition, and follow-up time in each study, are shown in Supplementary Table 1. The pooled data showed that GDFT significantly reduced AKI incidence over usual care \((OR 0.62, 95\% CI 0.47 to 0.80, p < 0.001; Figure 3)\). The heterogeneity was moderate \((I^2 = 50\%)\). No sign of significant publication bias was observed (Supplementary Figure 1). The sensitivity analysis considering only low risk of bias studies showed the same result: compared with usual care, GDFT reduced the risk of renal injury in critically ill patients \((OR 0.66, 95\% CI 0.54 to 0.82, p < 0.001; I^2 = 13\%)\).

Subgroup analyses showed that in both postoperative and medical patients, the AKI incidences were lower in the GDFT group \((postoperative patients: OR 0.68, 95\% CI 0.54 to 0.87, p = 0.002; medical patients: OR 0.39, 95\% CI 0.17 to 0.86, p = 0.02; Figure 4)\). The heterogeneity was low in the subgroup of postoperative patients \((I^2 = 27\%)\) but higher in the subgroup of medical patients \((I^2 = 70\%)\). In medical patients, we further performed a subgroup analysis of patients with septic shock, which showed no effect of GDFT on AKI with a lower heterogeneity \((OR 0.66, 95\% CI 0.39 to 1.14, p = 0.14; I^2 = 22\%)\). A significant AKI reduction was observed in studies that adopted dynamic indicators \((including SVV, PPV, SV change, IVC collapsibility and distensibility) as fluid therapy targets \((OR 0.48, 95\% CI 0.30 to 0.77, p = 0.002; I^2 = 58\%); Figure 5)\), instead of these studies with EGDT \((OR 0.55, 95\% CI 0.25 to 1.24, p = 0.15; I^2 = 62\%); Figure 5) or the other protocols \((OR 0.74, 95\% CI 0.53 to 1.01, p = 0.06; I^2 = 25\%); Figure 5)\). In addition, the pooled data from RCTs \((OR 0.78, 95\% CI 0.65 to 0.95, p = 0.01; I^2 = 12\%); Figure 6) and non-RCTs \((OR 0.37, 95\% CI 0.27 to 0.51, p < 0.001; I^2 = 47\%); Figure 6) both showed a preventive effect of GDFT on AKI in critically ill patients.

RRT support

Thirteen \((n = 5,709, 2,884\) in the GDFT group and \(2,825\) in the control group) of the 28 included studies reported pooled analysis showing GDFT did not decrease the requirement for RRT \((OR 0.88, 95\% CI 0.74 to 1.05, p = 0.17; I^2 = 50\%); Supplementary Figure 2) in critically ill patients.

Fluid administration (L)

Of the 28 included studies, 22 \((n = 11,965, 5,983\) in the GDFT group and \(5,982\) in the control group) reported intravenous fluids at different time points. According to the different record times of fluid administration, the 22 studies were divided into three subgroups: within the
initial 6 h, more than 6 h and less than or equal to 24 h, and more than 24 h. The pooled data from 9 studies ($n=5,058; 2,526$ in the GDFT group and $2,532$ in the control group) showed that GDFT tended to increase the volume of fluid administration within the initial 6 h, but there was no significant difference between groups (MD $0.27$, 95% CI $0.04$ to $0.59$, $p=0.09$; Supplementary Figure 3). The heterogeneity was high.

The pooled data from 13 studies ($n=2,261; 1,141$ in the GDFT group and $1,120$ in the control group) showed that GDFT had no effect on fluid administration from 6 to 24 h (MD $0.34$, 95% CI $0.14$ to $0.81$, $p=0.16$; $I^2=98$% ; Supplementary Figure 3). However, the cumulative fluid administration in the GDFT group was less than that in the control group after 24 h ($n=4,646$; $2,316$ in the GDFT group and $2,330$ in the control group), with high heterogeneity (MD $-0.45$, 95% CI $-0.71$ to $-0.19$, $p<0.001$; $I^2=90$% ; Supplementary Figure 3).

**Vasopressor requirements**

For this outcome, 12 studies reported the use of vasopressors ($n=6,252; 3,116$ in the GDFT group and $3,136$ in the control group). Compared with the control group, patients in the GDFT group seemed to use more vasopressors, but the difference was not significant (OR $1.23$, 95% CI $1.00$ to $1.52$, $p=0.05$; $I^2=58$%; Supplementary Figure 4).

**Discussion**

This systematic review is the first to focus on the effect of GDFT on renal function in critically ill patients. Pooled data demonstrated that the incidence of AKI was reduced by GDFT in critical illness. This result was confirmed by the sensitivity analysis enrolling only low-risk-of-bias trials and the pooled data from RCTs. Subgroup analyses showed that both postoperative and medical patients benefited from GDFT, and the reduction in AKI was significant in GDFT aimed at dynamic indicators. However, GDFT was not associated with a reduction in RRT support.

Critically ill patients are at high risk of AKI, which is closely associated with poor prognosis. The most frequent causes of AKI in critical illness are sepsis, hypovolemia, direct nephrotoxicity, and major surgery [45]. AKI is believed to be initially preventable and reversible [46]. Fluid therapy is a key component of the prevention of AKI, and the aim is to correct hypovolemia and restore organ perfusion in addition to avoiding further nephrotoxic insults. Because routine hemodynamic measurements poorly predict volume status and renal

| Study or Subgroup | GDF T | Control | Odds Ratio | 95% CI |
|-------------------|-------|---------|------------|--------|
| Froghi 2022       | 16    | 30      | 1.00       | (0.36, 2.76) |
| Goepfert 2013     | 3     | 46      | 0.33       | (0.08, 1.34) |
| Huang 2018        | 3     | 25      | 0.18       | (0.04, 0.76) |
| Jhanji 2010       | 3     | 45      | 0.25       | (0.06, 0.98) |
| Jin 2018          | 32    | 131     | 0.54       | (0.30, 0.94) |
| Kanji 2014        | 65    | 95      | 0.12       | (0.05, 0.33) |
| Lin 2006          | 42    | 108     | 0.52       | (0.30, 0.88) |
| Liu 2016          | 0     | 48      | Not estimable |        |
| Luo 2017          | 3     | 73      | 0.47       | (0.11, 1.96) |
| MacDonald 2019    | 9     | 144     | 0.80       | (0.32, 1.99) |
| McKendry 2004     | 1     | 89      | 0.31       | (0.03, 3.05) |
| Muskatavern 2021  | 4     | 102     | 2.04       | (0.37, 11.40) |
| Pan 2019          | 50    | 103     | 0.42       | (0.22, 0.80) |
| Parke 2021        | 96    | 358     | 0.88       | (0.63, 1.22) |
| Pearsure 2014     | 17    | 366     | 0.90       | (0.50, 1.98) |
| Pestaña 2014      | 8     | 72      | 0.85       | (0.31, 2.34) |
| Schmid 2016       | 53    | 92      | 1.24       | (0.69, 2.23) |
| Suzuki 2014       | 9     | 53      | 0.56       | (0.21, 1.49) |
| Thomson 2014      | 8     | 123     | 0.28       | (0.12, 0.64) |
| Waal 2021         | 12    | 246     | 1.16       | (0.49, 2.71) |
| Wang 2021         | 6     | 66      | 0.86       | (0.22, 1.96) |
| Yealy 2014        | 12    | 439     | 1.14       | (0.50, 2.60) |

**Figure 3.** Forest plot of the effect of GDFT on AKI incidence without time limit. AKI: Acute kidney injury; GDFT: goal-directed fluid therapy; M-H: Mantel–Haenszel; CI: confidence interval.

**Table 3.** Forest plot of the effect of GDFT on AKI incidence without time limit. AKI: Acute kidney injury; GDFT: goal-directed fluid therapy; M-H: Mantel–Haenszel; CI: confidence interval.
blood flow in critical illness, the GDFT approach has been proposed.

Our study found that in comparison with usual care, GDFT reduced the incidence of AKI in critically ill patients. However, moderate heterogeneity limits the credibility of the results. Several questions remain unanswered, such as kind of patients, protocolized goals, and the impact of the quality of included studies. Therefore, we first performed sensitivity analysis enrolling only low-risk-of-bias trials. This showed the same result with low heterogeneity. Then, subgroup analysis of RCTs further confirmed the main result. In addition, subgroup analyses concerning postoperative versus medical patients and different fluid therapy targets were also performed.

The subgroup analysis of populations showed that GDFT significantly reduced AKI in both postoperative and medical patients. Consistently, a recent meta-analysis, including 65 studies with 9,306 adult patients undergoing major surgery and noncritical illness, which reported a marked decrease in the renal injury rate in the perioperative goal-directed therapy group [9]. It is worth noting that we found the preventive effect on AKI in medical patients. In fact, only six included study populations were medical patients. They were all shock patients, and half of them had septic shock. A further subgroup analysis of patients with septic shock showed no effect of GDFT on AKI. Similarly, a previous multicenter large sample RCT did not find any protective effect of EGDT on renal function in septic shock patients [14]. In patients/animals with septic shock, global renal blood flow is preserved or even increased [47]. In contrast, decreases in glomerular filtration pressure, inflammatory tubules and microvascular injury result in renal

Figure 4. Pooled AKI incidence of subgroup analysis concerning postoperative and medical patients. AKI: Acute kidney injury; M-H: Mantel–Haenszel; CI: confidence interval.
dysfunction in sepsis [48]. Therefore, optimizing hemodynamics has limited preventive effects on septic AKI.

The subgroup analysis regarding targets showed that GDFT based on dynamic indicators significantly reduced AKI incidence, rather than EGDT and other protocols. However, the heterogeneity in the ‘dynamic indicators’ subgroup was relatively high and two large studies [27,40] which showed preferable results for GDFT in this subgroup were non-RCTs. These can be a risk of bias and weak the strength of the evidence. About EGDT, it was first introduced by Rivers et al and mainly used in patients with sepsis [11]. The effect of EGDT on prognosis, including AKI and mortality, is still controversial [10,14,25,33]. In summary, GDFT aimed at dynamic indicators may be an effective way to protect renal function in critically ill patients.

In addition, there was no effect of GDFT on RRT support. Consistently, a previous meta-analysis found no differences in the RRT rate between the standard EGDT and usual care groups in patients with severe sepsis and septic shock [49]. These results suggested that GDFT did not improve the deterioration of renal function in patients who had already developed AKI. Consistent with this view, one previous study reported that GDFT did not reduce the persistence of AKI beyond 72 h for patients in the early stage of AKI [15].
summary, the beneficial effect of GDFT on renal function is more significant in patients without AKI.

We further analyzed the role of fluid administration and vasopressor requirements. The results demonstrated that although GDFT tended to increase fluid administration within the initial six hours compared with usual care, it was not substantially different between the groups in the initial 24 h. After 24 h, fluid administration was less common in the GDFT group. In addition, GDFT was associated with more vasopressor requirements. Using vasopressors for a short duration might meet the acute demand for oxygen delivery and limit the volume of fluid administration [7]. Guidelines recommend that accurate and timely fluid therapy improves organ function [50]. Excessive volume expansion is also associated with adverse outcomes, including renal dysfunction [51–53]. GDFT by means of fluids and vasopressors can minimize the time of low perfusion and spare unwarranted fluid therapy, which may contribute to the prevention of AKI.

The strengths of this study include broad search strategy, inclusion of extensive studies and the latest research with high quality of methodology. Moreover, unlike previous meta-analyses focused on the effect of goal-directed therapy on AKI in patients undergoing surgery [9], we are the first to focus on critically ill patients. In addition, we further performed sensitivity analysis and subgroup analyses, generating new hints for practical applications. In fact, all critically ill patients were at risk for AKI. GDFT aimed at dynamic parameters may be more helpful for AKI prevention but does not change the disease course.

This study has a number of limitations. First, the protocols of GDFT varied in the included studies, and the definitions of usual care may be different in different areas. This led to relatively high heterogeneity,
although the results remained consistent across sensitivity and subgroup analyses. Second, most of the included studies lacked baseline kidney function, that is, chronic kidney disease. Third, the included studies varied in definitions, and timeframes of AKI incidence were another limitation. Last, there may be potential publication bias.

Conclusions
In conclusion, this meta-analysis suggests that GDFT reduced the incidence of AKI in critical illness, including postoperative and medical patients. Sensitivity analysis enrolling only trials with a low risk of bias and subgroup analysis of RCTs confirmed this result. The reduction was significant in GDFT based on dynamic indicators, rather than EGDT and other protocols. However, there was no difference in RRT support between the groups. Fluid administration seemed to be higher in the GDFT group within the first 6 h but lower after 24 h. Moreover, GDFT was associated with more vasopressor requirements. Prompt, targeted resuscitation combined with fluid and vasopressors may contribute to the prevention of AKI.

Disclosure statement
The authors report no conflict of interest.

Funding
This work was supported by the Health and Family Planning Commission of Hebei Province, China [No: ZD20140134]. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ORCID
Chai Zhao http://orcid.org/0000-0002-5073-2766

Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article.

References
[1] Choi JG, Kim SY, Jeong M, et al. Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders. Pharmacol Ther. 2018;182:777–69.
[2] Kellum JA, Chawla LS, Keener C, et al. The effects of alternative resuscitation strategies on acute kidney injury in patients with septic shock. Am J Respir Crit Care Med. 2016;193(3):281–287.
[3] Deng Y, Yuan J, Chi R, et al. The incidence, risk factors and outcomes of postoperative acute kidney injury in neurosurgical critically ill patients. Sci Rep. 2017;7(1):4245.
[4] Bhvorac A, Yavas S, Subbiah S, et al. Long-term risk of mortality and acute kidney injury during hospitalization after major surgery. Ann Surg. 2009;249(5):851–858.
[5] Brienza N, Giglio MT, Dalfino L. Protocolized resuscitation and the prevention of acute kidney injury. Curr Opin Crit Care. 2012;18(6):613–622.
[6] Dalfino L, Giglio MT, Puntilllo F, et al. Haemodynamic goal-directed therapy and postoperative infections: earlier is better. A systematic review and meta-analysis. Crit Care. 2011;15(3):R154.
[7] Cecconi M, Corredor C, Arulkumaran N, et al. Clinical review: goal-directed therapy-what is the evidence in surgical patients? The effect on different risk groups. Crit Care. 2012;17(2):209.
[8] Brienza N, Giglio MT, Marucci M, et al. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med. 2009;37(6):2079–2090.
[9] Giglio M, Dalfino L, Puntilllo F, et al. Hemodynamic goal-directed therapy and postoperative kidney injury: an updated meta-analysis with trial sequential analysis. Crit Care. 2019;23(1):232.
[10] Lin SM, Huang CD, Lin HC, et al. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock. 2006;26(6):551–557.
[11] Rivers E, Nguyen B, Hvasad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med. 2001;345(19):1368–1377.
[12] de Oliveira CF, de Oliveira DS, Gottschald AF, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: an outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med. 2008;34(6):1065–1075.
[13] Ahmed W, Memon JI, Rehmani R, et al. Outcome of patients with acute kidney injury in severe sepsis and septic shock treated with early goal-directed therapy in an intensive care unit. Saudi J Kidney Dis Transpl. 2014;25(3):544–551.
[14] Yealy DM, Kellum JA, Huang DT, ProCESS Investigators, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370(18):1683–1693.
[15] Amendola CP, Silva JM, Jr Carvalho T, et al. Goal-directed therapy in patients with early acute kidney injury: a multicenter randomized controlled trial. Clinics (Sao Paulo). 2018;73:e327.
[16] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
[17] Higgins JP, Altman DG, Gotzsche PC, et al. The cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

Zhao L, Qian-mei W, Fan-yang L, et al. Effect of early goal-directed therapy on patients with moderate brain injury and traumatic shock. Clinical Misdiagnosis & Misdagnosis. 2016;29:80–83.

Biao H, Zhang M, Dabi H, et al. Clinical study on the value of early hemodynamic intervention in the management of hypovolemic shock with unknown cause. Journal of Chongqing Medical University. 2018;43:913–918.

Pan C, Liu J, Hu X. [Effect of goal-directed therapy bundle based on PiCCO parameters to the prevention and treatment of acute kidney injury in patients after cardiopulmonary bypass cardiac operation: a prospective observational study]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue. 2019;31(6):731–736.

Jin Y, Zhao H, Chen Y. Target-directed management strategy reduces complications in high-risk subjects undergoing cardiac and major vascular surgery. Int J Clin Exp Med. 2016;9:22241–22249.

Douglas IS, Alapat PM, Corl KA, et al. Fluid response evaluation in sepsis hypotension and shock: a randomized clinical trial. Chest. 2020;158(4):1431–1445.

Goepfert MS, Richter HP, Zu Eulenburg C, et al. Individually optimized hemodynamic therapy reduces complications and length of stay in the intensive care unit: a prospective, randomized controlled trial. Anesthesiology. 2013;119(4):824–836.

Investigators A, Group ACT, Peake SL, et al. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371(16):1496–1506.

Jhanji S, Vivian-Smith A, Lucena-Amaro S, et al. Haemodynamic optimisation improves tissue microvascular flow and oxygenation after major surgery: a randomised controlled trial. Crit Care. 2010;14(4):R151.

Kanji HD, McCallum J, Siorounis D, et al. Limited echocardiography-guided therapy in subacute shock is associated with change in management and improved outcomes. J Crit Care. 2014;29(5):700–705.

Latham HE, Bengtson CD, Satterwhite L, et al. Stroke volume guided resuscitation in severe sepsis and septic shock improves outcomes. J Crit Care. 2017;42:42–46.

Luo J, Xue J, Liu J, et al. Goal-directed fluid restriction during brain surgery: a prospective randomized controlled trial. Ann Intensive Care. 2017;7(1):16.

MacDonald N, Pearse RM, Murray PT, et al. The role of goal-directed therapy in the prevention of acute kidney injury after major gastrointestinal surgery: sub-study of the OPTIMISE trial. Eur J Anaesthesiol. 2019;36(12):924–932.

Martin D, Koti R, Gurusamy K, COLT study group, et al. The cardiac output optimisation following liver transplant (COLT) trial: a feasibility randomised controlled trial. HPB (Oxford). 2020;22(8):1112–1120.

McKendry M, McGloin H, Saberi D, et al. Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ. 2004;329(7460):258.

Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. N Engl J Med. 2015;372(14):1301–1311.

Musikatavorn K, Plitawanon P, Lumlertgul S, et al. Randomised controlled trial of ultrasound-guided fluid resuscitation of sepsis-induced hypoperfusion and septic shock. West J Emerg Med. 2021;22(2):369–378.

Parke RL, Gilder E, Gillham MJ, et al. A multicenter, open-label, randomized controlled trial of a conservative fluid management strategy compared with usual care in participants after cardiac surgery: the fluids after bypass study. Crit Care Med. 2021;49(3):449–461.

Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. JAMA. 2014;311(21):2181–2190.

Pestana D, Espinosa E, Eden A, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: a prospective, randomized, multicenter, pragmatic trial: POEMAS study (PeriOperative goal-directed therapy in major abdominal surgery). Anesth Analg. 2014;119(3):579–587.

Schmid S, Kapfer B, Heim M, et al. Algorithm-guided goal-directed haemodynamic therapy does not improve renal function after major abdominal surgery compared to good standard clinical care: a prospective randomised trial. Crit Care. 2016;20(1):50.

Suzuki S, Woinarski NC, Lipsey M, et al. Pulse pressure variation-guided fluid therapy after cardiac surgery: a pilot before-and-after trial. J Crit Care. 2014;29(6):992–996.

Thomson R, Meeran H, Valencia O, et al. Goal-directed therapy after cardiac surgery and the incidence of acute kidney injury. J Crit Care. 2014;29(6):997–1000.

Yu J, Zheng R, Lin H, et al. Global end-diastolic volume index vs CVP goal-directed fluid resuscitation for COPD patients with septic shock: a randomized controlled trial. Am J Emerg Med. 2017;35(1):101–105.

de Waal EEC, Frank M, Scheeren TWL, et al. Perioperative goal-directed therapy in high-risk abdominal surgery. A multicenter randomized controlled superiority trial. J Clin Anesth. 2021;75:110506.

Wang K, Sun SL, Wang XY, et al. Bioelectrical impedance analysis-guided fluid management promotes primary fascial closure after open abdomen: a randomized controlled trial. Mil Med Res. 2021;8(1):36.

Froghi F, Gopalan V, Anastasiou Z, et al. Effect of post-operative goal-directed fluid therapy (GDFT) on organ function after orthotopic liver transplantation: secondary outcome analysis of the COLT randomised control trial. Int J Surg. 2022;99:106265.

Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;294(7):813–818.

Blantz RC. Pathophysiology of pre-renal azotemia. Kidney Int. 1998;53(2):512–523.
alterations in the renal circulation. Semin Nephrol. 2015;35(1):64–74.

[48] John S. Lessons learned from kidney dysfunction: preventing organ failure. Med Klin Intensivmed Notfmed. 2020;115(Suppl 1):21–27.

[49] Jiang LB, Zhang M, Jiang SY, et al. Early goal-directed resuscitation for patients with severe sepsis and septic shock: a meta-analysis and trial sequential analysis. Scand J Trauma Resusc Emerg Med. 2016;24:23.

[50] Liu DW, Wang XT, Zhang HM, et al. Hemodynamic therapy for severe cases—Beijing consensus. Chin J Intern Med. 2015;54:248–271.

[51] Woodward CW, Lambert J, Ortiz-Soriano V, et al. Fluid overload associates with major adverse kidney events in critically ill patients with acute kidney injury requiring continuous renal replacement therapy. Crit Care Med. 2019;47(9):e753–e60.

[52] National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, et al. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–2575.

[53] Grams ME, Estrella MM, Coresh J, et al. Fluid balance, diuretic use, and mortality in acute kidney injury. Clin J Am Soc Nephrol. 2011;6(5):966–973.