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Protocol-Based Resuscitation for Septic Shock: A Meta-Analysis of Randomized Trials and Observational Studies

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Purpose: Owing to the recommendations of the Surviving Sepsis Campaign guidelines, protocol-based resuscitation or goal-directed therapy (GDT) is broadly advocated for the treatment of septic shock. However, the most recently published trials showed no survival benefit from protocol-based resuscitation in septic shock patients. Hence, we aimed to assess the effect of GDT on clinical outcomes in such patients.

Materials and Methods: We performed a systematic review that included a meta-analysis. We used electronic search engines including PubMed, Embase, and the Cochrane database to find studies comparing protocol-based GDT to common or standard care in patients with septic shock and severe sepsis.

Results: A total of 13269 septic shock patients in 24 studies were included [12 randomized controlled trials (RCTs) and 12 observational studies]. The overall mortality odds ratio (OR) [95% confidence interval (CI)] for GDT versus conventional care was 0.746 (0.631–0.883). In RCTs only, the mortality OR (95% CI) for GDT versus conventional care in the meta-analysis was 0.93 (0.75–1.16). The beneficial effect of GDT decreased as more recent studies were added in an alternative, cumulative meta-analysis. No significant publication bias was found.

Conclusion: The result of this meta-analysis suggests that GDT reduces mortality in patients with severe sepsis or septic shock. However, our cumulative meta-analysis revealed that the reduction of mortality risk was diminished as more recent studies were added.

Key Words: Sepsis, septic shock, shock, meta-analysis

INTRODUCTION

Severe sepsis and septic shock are complex systemic responses to infection and have immunologic, cardiovascular, and pulmonary implications. There have been numerous treatment strategies aimed at reversing pathophysiologic derangement in sepsis patients. Since its introduction in a landmark trial in 2001,[1] goal-directed therapy (GDT) has demonstrated significant survival benefits in sepsis. GDT focuses on the early initiation of monitoring measurements such as central venous pressure and lactate levels, as well as therapeutic maneuvers involving fluid, vasopressors, and transfusion. It was thus a reasonable decision to adopt early GDT in the Surviving Sepsis Campaign (SSC) international guidelines due to the accumulation of clinical evidence of its benefits.[2,3]

However, this method of treating patients with sepsis has been challenged by several recent multicenter trials. The ARISE trial[4] randomized 1600 early septic-shock patients divided into GDT and usual-care groups. The investigators found that there

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was no significant difference in 90-day mortality, duration of organ support, and length of hospital stay. Another multicenter trial comparing GDT to standard care was the ProCESS study,[5] which showed no differences in 90-day and 1-year all-cause mortality or in the need for organ support; this outcome was similar to that of the ARISE trial.

To evaluate the effect of GDT on mortality risk reduction, two meta-analyses were recently published.[6,7]

One advocated for the survival benefit of GDT,[6] while the other showed conflicting results with no difference observed in survival; in fact, an even worse outcome was associated with GDT in the early-lactate clearance subgroup of patients.[7]

Given such inconsistent results, we conducted a meta-analysis that included the most recent trials of GDT in patients with sepsis. In particular, we assessed the time-dependent changes in risk reduction of GDT by performing a cumulative meta-analysis.

MATERIALS AND METHODS

Ethics committee approval and patient informed consent were not required, as we conducted a meta-analysis of previously published studies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[8] and the Cochrane Handbook of Systematic Review of Interventions to perform the study.

Literature search

Two authors (Lee and Kim) independently conducted searches in PubMed, Embase, and the Cochrane Register of Controlled Trials databases during the period between the March 20, 2015 and the May 30, 2015 to identify all randomized clinical trials involving GDT in human subjects with septic shock. Search terms were "sepsis," "shock," "septic," "early goal-directed therapy," "EGDT," "central venous oxygen saturation," and "goal-directed resuscitation." Studies published from January 1992 to May 2015 were additionally included.

We also screened the references included in the articles and published systematic reviews during the same periods to identify other potentially eligible studies.

Inclusion criteria

We included prospective clinical trials conducted in adult patient populations with septic shock. Adults were defined as being over 17 years of age. The intervention was required to comprise GDT, defined as an explicit protocol encompassing the use of hemodynamic monitoring as well as manipulation of hemodynamic parameters to achieve predetermined hemodynamic endpoints. The goals regarding the hemodynamic parameters were different depending on the trials. We defined GDT as a treatment with a specific hemodynamic goal. We only included studies reporting mortality and excluded those reporting only physiological endpoints. Only English-language publications were reviewed.

Quality assessment

The quality of the included studies was determined by two independent assessors who had no role in the design, conduct, analysis, or reporting of any of the included studies. The Cochrane Collaboration tool was used to assess the risk of bias for the randomized studies across the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other sources of bias.

The RoBANS Tool 9 was used to assess the risk of bias for the observational, non-randomized studies across the following domains: selection of participants (selection bias), confounding variables (selection bias), measurement of intervention (performance bias), blinding for outcome assessment (detection bias), incomplete outcome (attrition bias), and selective outcome reporting (reporting bias).

Outcome measures

The primary outcome was overall mortality. If the study reported mortality at one time-point, we used only the data provided in the study for our analysis. If the study authors reported mortality at more than one time-point, we preferentially used hospital mortality data. Overall mortality was the only measure we used to compare the efficacy of GDT.

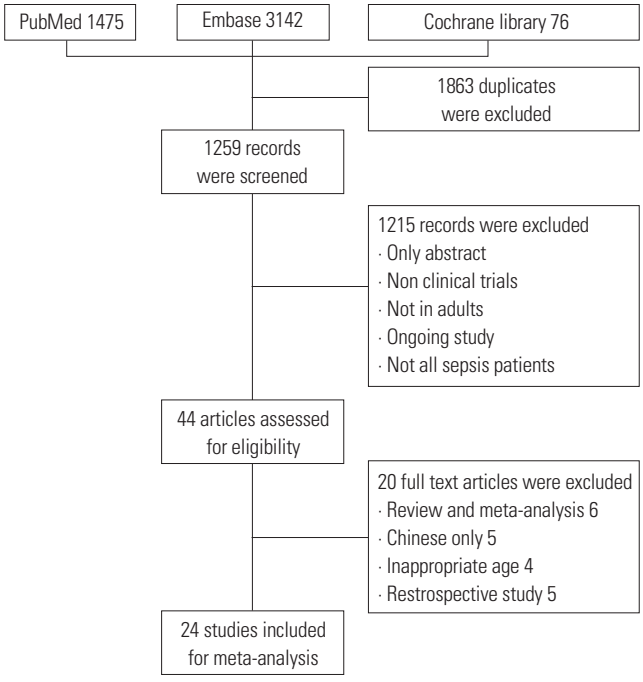

Fig. 1. Flow diagram showing results of search and reasons for exclusion of studies.

Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study

Study	Year	Study type	Initiation of enrollment	No. of patients (GDT/control)	Study population	Clinical setting	Goals in GDT group	Goals in control group	Timing of GDT	Endpoint
Tuchschmidt, et al.[14]	1992	RCT	Unknown	26/25	Adult patients with septic shock	ICU	CI>6 L/min/m^2 SBP>90 mm Hg	CI>3 L/min/m^2 SBP>90 mm Hg	6 hrs	Hospital mortality
Yu, et al.[15]	1993	RCT	Unknown	30/22	Adult patients with sepsis or septic shock	ICU	DO_2I>600 mL/min/m^2 SBP>100 mm Hg	DO_2I 450–550 mL/min/m^2	24 hrs	30 days mortality
Hayes, et al.[13]	1994	RCT	Unknown	50/50	Adult patients with septic shock	ICU	CI>4.5 L/min/m^2 DO_2I>600 mL/min/m^2 VO_2>170 mL/min/m^2	Usual care	Unclear	Hospital mortality
Gattinoni, et al.[16]	1995	RCT	1991	124/57	Adult patients with septic shock or septic syndrome	ICU	CI>4.5 L/min/m^2 or SvO_2>70% MBP>65 mm Hg CVP 8–12 mm Hg UO>0.5 mL/kg/hr	CI 2.5–3.5 L/min/m^2 MBP>65 mm Hg CVP 8–12 mm Hg UO>0.5 mL/kg/hr	Unclear	180 days mortality
Alía, et al.[17]	1999	RCT	1993	31/32	Adult patients with severe sepsis or septic shock	ICU	DO_2I>600 mL/min/m^2 MBP>60 mm Hg	DO_2I>330 mL/min/m^2 MBP>60 mm Hg	Unclear	ICU mortality
Rivers, et al.[1]	2001	RCT	1997	130/133	Adult patients with severe sepsis, septic shock or sepsis syndrome	ED	SvO_2>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	CVP 8–12 mm Hg MBP 65–90 mm Hg UO>0.5 mL/kg/hr	6 hrs	Hospital mortality
Gao, et al.[25]	2005	Prospective observational	2004	52/49	Adult patients with septic shock	Ward ICU	Compliant to EGDT protocol; SvO_2>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Noncompliant to EGDT protocol	6 hrs	Hospital mortality
Micek, et al.[19]	2006	Before and after	2004	60/60	Adult patients with septic shock	ICU	Add an order set for EGDT protocol; SvO_2>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before adding an order set for EGDT protocol	6 hrs	Hospital mortality
Lin, et al.[29]	2006	RCT	2003	108/116	Adult patients with septic shock	ICU	CVP 8–12 mm Hg, MAP>65 mm Hg, UO>0.5 mL/kg/hr	Usual care	6 hrs	Hospital mortality
Nguyen, et al.[26]	2007	Prospective observational	2003	77/253	Adult patients with septic shock	ED ICU	After education of therapeutic target of EGDT; $ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before education of EGDT	6 hrs	Hospital mortality

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Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study (Continued)

Study	Year	Study type	Initiation of enrollment	No. of patients (GDT/control)	Study population	Clinical setting	Goals in GDT group	Goals in control group	Timing of GDT	Endpoint
Jones, et al.[12]	2007	Prospective interventional	2005	77/79	Adult patients with septic shock	ED ICU	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before education of EGDT	6 hrs	Hospital mortality
Zambon, et al.[2]	2008	Prospective observational	2005	44/17	Adult patients with septic shock	ICU	Compliant to target of EGDT; $ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Not compliant to target of EGDT	6 hrs	Hospital mortality
Ferrer, et al.[23]	2008	Before and after	2006	1465/854	Adult patients with septic shock	ICU	After education of EGDT protocol; $ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before education of EGDT protocol	6 hrs	Hospital mortality
MacRedmond, et al.[24]	2010	Prospective observational cohort	2008	37/37	Adult patients with septic shock	ED ICU	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before EGDT protocol	6 hrs	Hospital mortality
Puskarich, et al.[27]	2009	Before and after	2005	206/79	Adult patients with septic shock	ED	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before EGDT protocol	6 hrs	1 yr mortality
Crowe, et al.[30]	2010	Prospective observational cohort	2007	183/123	Adult patients with septic shock	ED	$ScvO_2$>70% (not continuous) CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before EGDT protocol	6 hrs	Hospital mortality
De Miguel-Yanes, et al.[28]	2009	Observational cohort	2007	50/53	Adult patients with septic shock	ED	After education of EGDT; $ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before education of EGDT	6 hrs	Hospital mortality
Castellanos-Ortega, et al.[3]	2010	Quasi-experimental study	2005	384/96	Adult patients with septic shock	ICU	After education of EGDT; $ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Before education of EGDT	6 hrs	Hospital mortality
Jones, et al.[18]	2010	RCT	2007	150/150	Adult patients with septic shock	ED	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Lactate clearance CVP>8 mm Hg MBP>65 mm Hg	Unclear	Hospital mortality
Coba, et al.[20]	2011	Prospective cohort	2006	64/434	Adult patients with septic shock	ED ICU	Compliant within 6 hrs to EGDT protocol; $ScvO_2$ 70%, CVP>8 mm Hg, MAP>65 mm Hg	Not compliant	6 hrs	Hospital mortality

Table 1. Characteristics of Included Studies with Published Year, Study Type, Initiation of Enrollment Year, Number of Patients of Each Group, Study Population, Clinical Settings, Treatment Goals in Each Group, Timing of GDT, and Endpoint of the Study (Continued)

Study	Year	Study type	Initiation of enrollment	No. of patients (GDT/control)	Study population	Clinical setting	Goals in GDT group	Goals in control group	Timing of GDT	Endpoint
Andrews, et al.[21]	2014	RCT	2012	53/56	Adult patients with septic shock	ED ward ICU	Simplified Severe Sepsis Protocol: Hb>7 initial 2 L bolus of NS (within 1 hr), if, CVP<3 mm Hg; 2 L loading MAP>65 mm Hg, dopamine infusion 10 mcg/kg/min	Usual care	6 hrs	Hospital mortality
ARiSe[4]	2014	RCT	2008	796/804	Adult patients with septic shock	ED	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Usual care	6 hrs	90 days mortality
ProCESS[5]	2014	RCT	2008	439/456	Adult patients with septic shock	ED	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Usual care	6 hrs	60 days mortality
ProMISe[22]	2015	RCT	2012	623/620	Adult patients with septic shock	ED ICU	$ScvO_2$>70%, CVP 8–12 mm Hg, MAP 65–90 mm Hg, UO>0.5 mL/kg/hr	Usual care	6 hrs	90 days mortality

RCT, randomized controlled trial; GDT, goal-directed therapy; CI, cardiac index; SBP, systolic blood pressure; DO_2I, oxygen delivery index; VO_2, oxygen consumption; SvO_2, mixed venous oxygen saturation; $ScvO_2$, central venous oxygen saturation; CVP, central venous pressure; MAP, mean arterial pressure; UO, urine output; ED, emergency department; hr, hour; ICU, intensive care unit; MBP, mean blood pressure; EGDT, early goal-directed therapy.

Statistical analysis

Whether heterogeneity between study effects was significant or not was evaluated by using the Q statistical value obtained via chi-squared distribution analysis in order to identify appropriate studies. The random effect model was adopted where the *p*-value of the Q statistic for the accumulated effects was greater than 0.1.[9] The odds ratio (OR) along with the 95% confidence interval (CI) of the overall mortality are presented. Publication bias was investigated by using a funnel plot and Egger and Begg's statistical tests.[10,11] The funnel plots did not indicate publication biases, a finding that was further confirmed in the Egger and Begg's tests, which yielded *p*-values greater than 0.05. All data analyses were performed using Comprehensive Meta-Analysis version 2.0 (Biostat, Inc., Englewood, NJ, USA).

RESULTS

Identification of eligible trials

In the initial search, we identified 4693 articles (Fig. 1). After the removal of 1863 duplicates, we reviewed 1259 titles and abstracts and eliminated 1215 articles not meeting the study inclusion criteria. Two investigators reviewed 44 full-text articles and subsequently excluded 20 that did not meet the inclusion criteria: six articles were reviews or meta-analyses, five were published in Chinese only, four were inappropriate owing to the age range of those studied (i.e., children or geriatric patients), and five were retrospective studies. Randomized controlled trials (RCTs), prospective cohort studies, and before-and-after studies were included in the analysis.

Characteristics of included trials

Twenty-four studies fulfilled the inclusion criteria: 12 each of RCTs and non-RCTs. In Table 1, the characteristics of the included trials are summarized. The regions where the studies were performed included the United States, Canada, Spain, Italy, Germany, Taiwan, Africa, and Australia; thus, there was a broad international distribution. The population age targeted by Jones, et al.[12] was over 17 years, while that targeted by Hayes, et al.[13] was over 21 years. The protocols for GDT were variable. The early studies[13-17] targeted the oxygen delivery index, cardiac index, and oxygen consumption. The therapeutic targets of the study by Rivers, et al.[1] included SvO_2 (mixed venous oxygen saturation) >70, central venous pressure 8–12, and mean arterial pressure >65. The later studies mostly followed the GDT protocol of Rivers, et al.,[1] and one of the studies modified the protocol by using lactate instead of SvO_2.[18] The target time for therapy administration was generally within 6 hours except in five studies; four[3,13,15,16] had unclear target times and one[14] targeted 24 hours. The years of publication of these studies were between 1992 and 2015.

Risks of bias in the included studies

The details of the risks of bias, summarized in Fig. 2, are each

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categorized into RCTs and non-RCTs. The RCTs (Fig. 2A) mostly exhibited a low risk of bias,[4,5,13,14,16,17,19-22] although the risk in two studies was unclear.[15] Adequate randomized sequences were generated in six trials, while proper randomization was questionable in two studies. None of the RCTs were double-blinded; blinding of patients and clinicians is extremely difficult when treating for septic shock, especially when applying GDT protocols. However, we concluded that the primary outcome (mortality) was seldom influenced by blinding the study. Biases related to reporting were low; other biases were unclear.

Almost all non-RCTs (Fig. 2B) were at high risk of selection bias except in four studies.[12,19,23,24] These four studies were conducted consecutively, and their data were collected prospectively. All non-RCTs were at a high risk of containing confounding variables. Four non-RCTs were before-and-after investigations,[19,23,25] while the others were prospective observational studies. We assumed that the learning effects were clear to the researchers when performing the before-and-after studies using the GDT protocol. In the prospective observational studies, major confounders were confirmed, although adjusting for the confounders was difficult. The bias in measurements was relatively low as the primary outcome was patient mortality.

Overall mortality

A total of 13269 patients were available for the analysis of our primary endpoint. Overall mortality in the GDT and control groups was 1717 of 5259 patients and 1638 of 4655 patients, re-

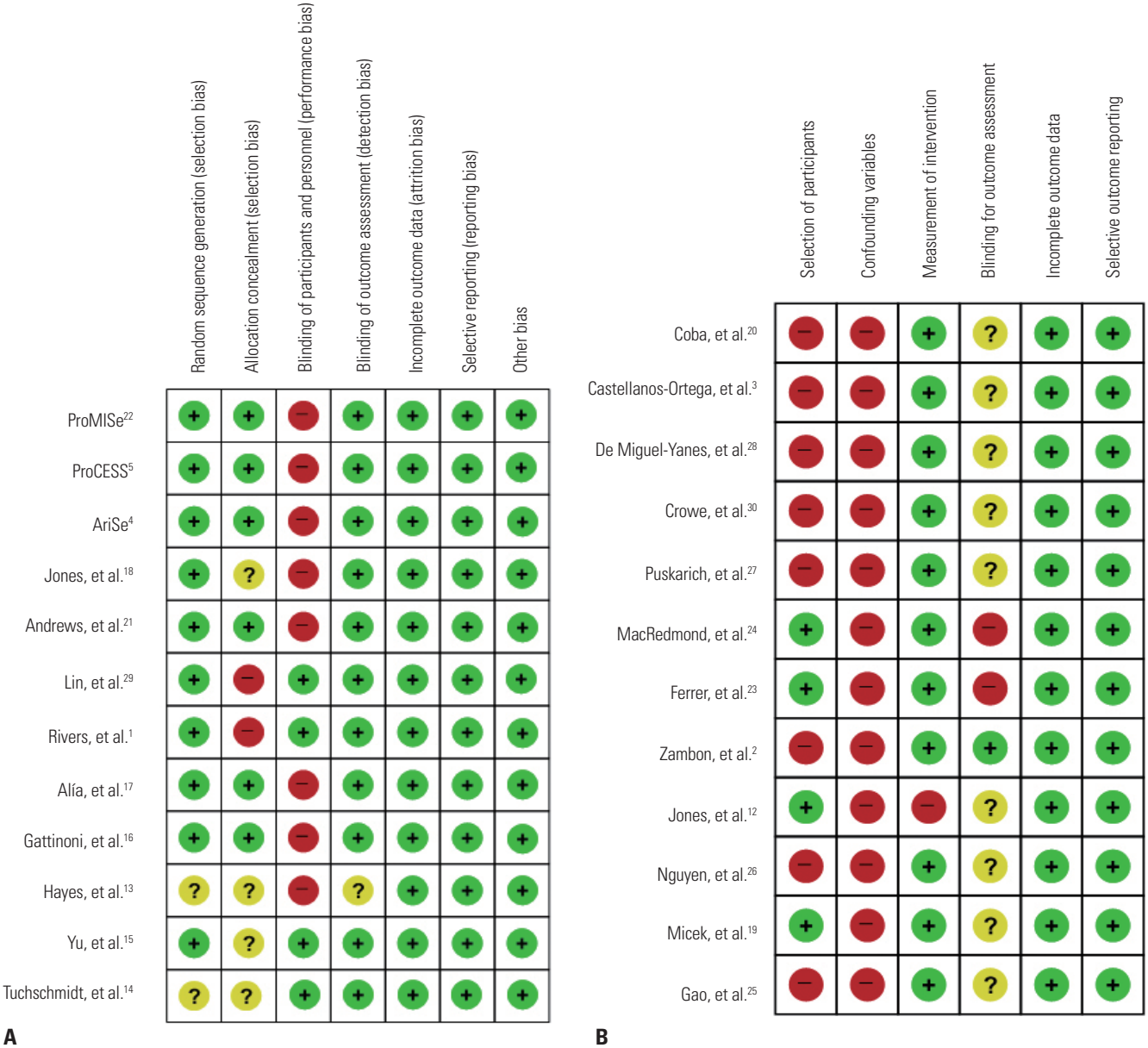

Fig. 2. (A) Risk of bias summary of RCTs with Cochrane Collaboration tool. (B) Risk of bias summary of non-RCTs with Cochrane Collaboration tool. RCTs, randomized controlled trials.

spectively. Overall, GDT significantly reduced overall mortality in the random-effects model (OR, 0.746; 95% CI, 0.631–0.883; *p*-value for heterogeneity <0.0001; I^2=57.71%) (Fig. 3). The results of the subgroup analyses are presented in Table 2.

RCT-only meta-analysis

In the subgroup analysis (Table 2), we evaluated RCT studies only.[1,4,5,13-18,21,22,29] GDT had no benefit regarding overall mortality compared to the results of all studies including non-RCTs (OR, 0.929; 95% CI, 0.747–1.155; *p*-value for heterogeneity=0.024; I^2=50.07%) (Fig. 4). This result contrasted with that of the analysis of all studies.

Cumulative statistics

We indexed the studies based on when each was performed and then categorized them into three groups: 2001–2003,[19,25,29] 2004–2007,[2,3,12,18-20,23,25,27-30] and 2008 or later.[4,5,21,22,24] This classification was according to the SSC publication update. We then conducted a cumulative meta-analysis. The results revealed that the effectiveness of each GDT was decreasing (Fig. 5) and was

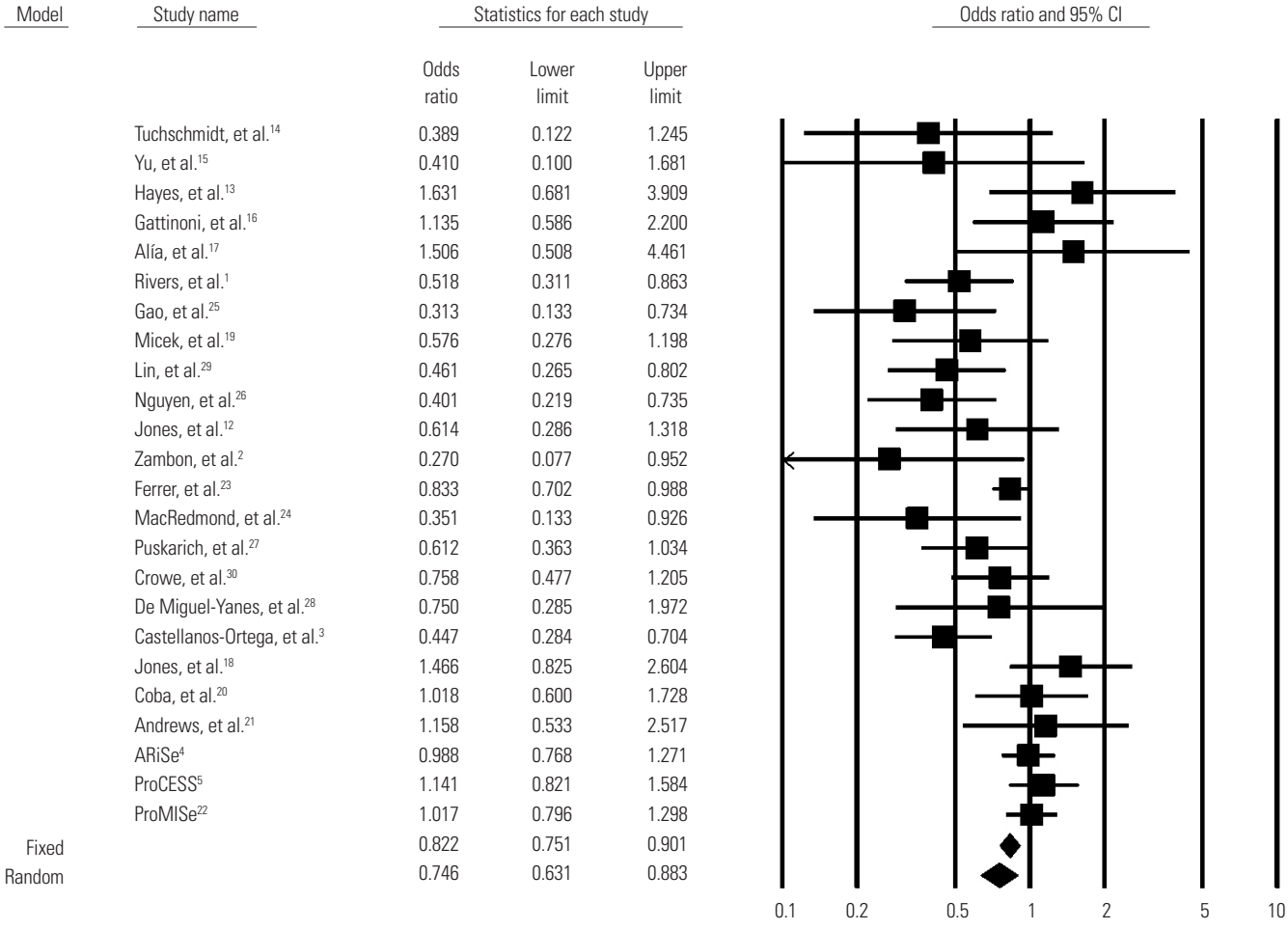

Fig. 3. Forest plot of the effectiveness of goal-directed therapy on overall mortality including RCTs and non-RCTs. RCTs, randomized controlled trials; CI, confidence interval.

Table 2. Subgroups Based on Study Type and Initiation Year

Subgroups	No. of studies	No. of patients	OR (95% CI)	*p* value	I^2 (%)
All trials	24	13269	0.75 (0.63–0.88)	<0.0001	57.71
Study type					
RCTs	12	6521	0.93 (0.75–1.16)	0.024	50.07
Non-RCTs	12	6748	0.60 (0.48–0.76)	0.031	48.13
Initiation of enrollment					
2001–2003	3	817	0.66 (0.44–0.98)	0.041	53.31
2004–2007	11	4472	0.69 (0.55–0.88)	0.003	51.88
2008–2015	5	3921	1.01 (0.87–1.17)	0.899	23.63

RCTs, randomized controlled trials; OR, odds ratio; CI, confidence interval.

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comparable with the subgroup analysis based on the study initiation year (Fig. 6).

Subgroup analysis based on the year of enrollment

In the subgroup analysis (Table 2), we evaluated the initiation year of the study enrollment and grouped studies into three pe-

Model	Study name	Odds ratio	Lower limit	Upper limit	Z-value	*p*-value
	ProMISe[22]	1.017	0.796	1.298	0.132	0.895
	ProCESS[5]	1.141	0.821	1.584	0.785	0.432
	ARiSe[4]	0.988	0.768	1.271	-0.097	0.922
	Andrews, et al.[21]	1.158	0.533	2.517	0.370	0.711
	Jones, et al.[18]	1.466	0.825	2.604	1.303	0.193
	Lin, et al.[29]	0.461	0.265	0.802	-2.743	0.006
	Rivers, et al.[1]	0.518	0.311	0.863	-2.529	0.011
	Alía, et al.[17]	1.506	0.508	4.461	0.739	0.460
	Gattinoni, et al.[16]	1.135	0.586	2.200	0.376	0.707
	Hayes, et al.[13]	1.631	0.681	3.909	1.098	0.272
	Yu, et al.[15]	0.410	0.100	1.681	-1.238	0.216
	Tuchschmidt, et al.[14]	0.389	0.122	1.245	-1.591	0.112
Fixed		0.963	0.846	1.097	-0.568	0.570
Random		0.929	0.747	1.155	-0.663	0.507

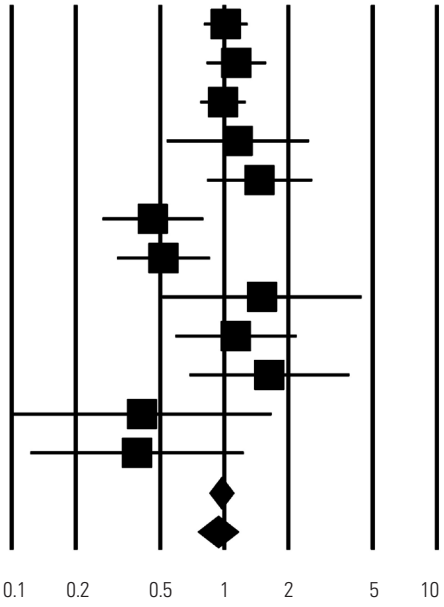

Fig. 4. Forest plot of the effectiveness of goal-directed therapy on overall mortality including only RCTs. RCTs, randomized controlled trials; CI, confidence interval.

Model	Study name	Point	Lower limit	Upper limit
	Lin, et al.[29]	0.461	0.265	0.802
	Nguyen, et al.[26]	0.433	0.288	0.651
	Gao, et al.[25]	0.407	0.282	0.589
	Micek, et al.[19]	0.437	0.314	0.607
	Jones, et al.[12]	0.461	0.340	0.623
	Zambon, et al.[2]	0.448	0.334	0.600
	Puskarich, et al.[27]	0.482	0.373	0.623
	Castellanos-Ortega, et al.[3]	0.474	0.379	0.592
	Ferrer, et al.[23]	0.527	0.397	0.699
	Coba, et al.[20]	0.568	0.437	0.739
	Crowe, et al.[30]	0.592	0.469	0.748
	De Miguel-Yanes, et al.[28]	0.601	0.482	0.750
	Jones, et al.[18]	0.639	0.508	0.804
	MacRedmond, et al.[24]	0.623	0.496	0.782
	ARiSe[4]	0.658	0.533	0.813
	ProCESS[5]	0.692	0.565	0.848
	ProMISe[22]	0.722	0.599	0.870
	Andrews, et al.[21]	0.736	0.614	0.882
Random		0.736	0.614	0.882

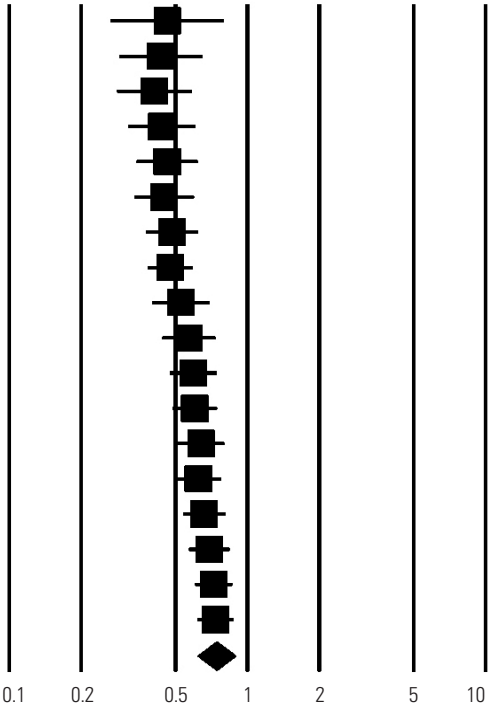

Fig. 5. Cumulative forest plot of RCTs and non-RCTs published after 2001. RCTs, randomized controlled trials; CI, confidence interval.

riods; period 1, before 2003; period 2, 2004–2007; and period 3, 2008–2015. This categorization was to analyze the change of clinical performance with time passage, and the results showed that the ORs approached values of 1 as time progressed (period 1, 0.661; period 2, 0.693; period 3, 1.010). We surmised that the difference between the effectiveness of GDT and usual care has decreased since 2001, simultaneously with the introduction of EGDT. Table 3 shows the amount of fluid administration within the first 6 hours in the recent RCTs. In the most recent study, the amount of fluid administration was not statistically different between the two groups, GDT and usual care.

Publication bias

We detected no evidence of publication bias as determined by the funnel plot both visually (Fig. 7) and statistically (p=0.359 by the Begg's test); we also checked the RCTs alone (p=0.837 using Begg's test) (Fig. 8).

DISCUSSION

In this meta-analysis, 12 RCTs and 12 non-RCTs were analyzed to compare overall mortality between GDT and non-GDT strategies. GDT remains an effective treatment modality for reducing the mortality rate among septic shock patients. Prospective and retrospective studies accumulated over the years verify the efficacy of the GDT protocol in reducing mortality among patients in septic shock. However, the differences in outcome between GDT and standard care have been decreasing according to recent trials.

A concrete form of GDT focusing on early therapeutic measures involving fluid, vasopressors, and transfusion to meet pre-

Study name	Subgroup	Statistics for each study		
		Odds ratio	Lower limit	Upper limit
Tuchschmidt, et al.[14]	Period 1	0.389	0.122	1.245
Yu, et al.[15]	Period 1	0.410	0.100	1.681
Hayes, et al.[13]	Period 1	1.631	0.681	3.909
Gattinoni, et al.[16]	Period 1	1.135	0.586	2.200
Alía, et al.[17]	Period 1	1.506	0.508	4.461
Rivers, et al.[1]	Period 1	0.518	0.311	0.863
Lin, et al.[29]	Period 1	0.461	0.265	0.802
Nguyen, et al.[26]	Period 1	0.401	0.219	0.735
	Fixed	0.620	0.481	0.799
	Random	0.661	0.444	0.983
Gao, et al.[25]	Period 2	0.313	0.133	0.734
Micek, et al.[19]	Period 2	0.576	0.276	1.198
Jones, et al.[12]	Period 2	0.614	0.286	1.318
Zambon, et al.[2]	Period 2	0.270	0.077	0.952
Ferrer, et al.[23]	Period 2	0.833	0.702	0.988
Puskarich, et al.[27]	Period 2	0.612	0.363	1.034
Crowe, et al.[30]	Period 2	0.758	0.477	1.205
De Miguel-Yanes, et al.[28]	Period 2	0.750	0.285	1.972
Castellanos-Ortega, et al.[3]	Period 2	0.447	0.284	0.704
Jones, et al.[18]	Period 2	1.466	0.825	2.604
Coba, et al.[20]	Period 2	1.018	0.600	1.728
	Fixed	0.761	0.669	0.865
	Random	0.693	0.546	0.879
MacRedmond, et al.[24]	Period 3	0.351	0.133	0.926
Andrews, et al.[21]	Period 3	1.158	0.533	2.517
ARiSe[4]	Period 3	0.988	0.768	1.271
ProCESS[5]	Period 3	1.141	0.821	1.584
PreMISe[22]	Period 3	1.017	0.796	1.298
	Fixed	1.010	0.869	1.173
	Random	1.003	0.833	1.208

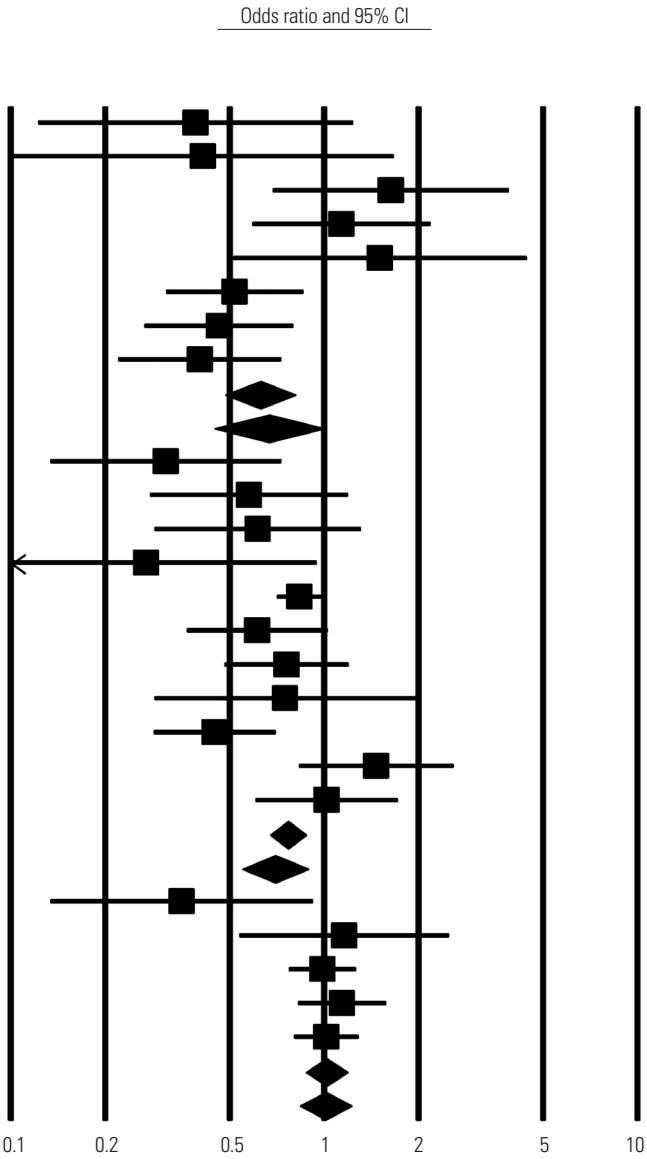

Fig. 6. Subgroup analysis, forest plot by study initiation year (period 1, before 2003; period 2, 2004–2007; period 3, 2008–2015). CI, confidence interval.

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Table 3. The Amount of Fluid Administration for First 6 Hours, Unit Is Presented As mL (Mean±Standard Deviation)

Author (study period)	EGDT	Control	*p* value
ProCESS (2011–2014)[5]	2805±1957	2783±1880	0.818
ARiSe (2008–2014)[4]	1964±1415	1713±1401	0.004*
ProMISe (2008–2013)[22]	2226±1443	2022±1271	0.001*

EGDT, early goal-directed therapy.
*Statistically significant, *p*-value<0.05.

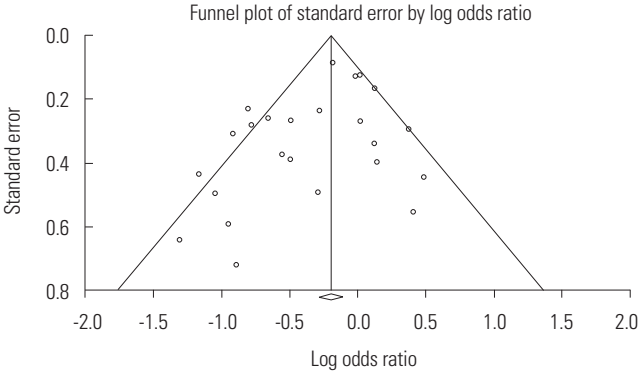

Fig. 7. Funnel plot of overall trials, RCTs and non-RCTs (*p*-value=0.359). RCTs, randomized controlled trials.

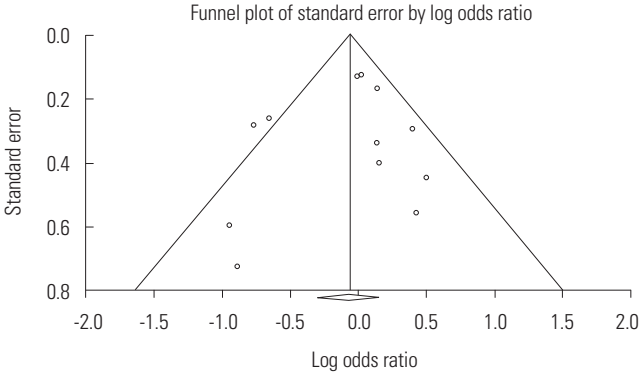

Fig. 8. Funnel plot of RCTs (*p*-value=0.837). RCTs, randomized controlled trials.

specified targets was introduced by a highly influential single-center trial performed by Rivers et al.,[1] although its primitive resuscitation protocol had been attempted beforehand.[13-17] They administered approximately 5 liters of fluid in the first 6 hours of resuscitation, resulting in a 16% improvement of in-hospital survival in severe sepsis and septic shock patients.

Although the efficacy of GDT remains a matter of debate, it has been rapidly integrated into clinical practice as a form of the sepsis bundle due to its definite survival benefit, and its clinical efficacy was established via subsequent trials.[27] In recent years, it has become less apparent whether GDT has any advantage for survival of patients with severe sepsis.[4,5,22] Investigators who published the latest meta-analyses, including RCTs, have already pronounced the end of the GDT era. However, further research is required to identify the efficacy of GDT for resuscitation of patients with sepsis and to re-evaluate the effect of GDT in clinical practice.

In our study, GDT showed no additional efficacy when analyzing RCTs only. However, in the overall analysis of prospective studies, including observational studies, GDT is effective in reducing mortality in sepsis patients. This finding is striking, as heterogeneous results from RCTs and observational studies could be the reason for detecting inconsistent effects of GDT in sepsis patients. The most recent meta-analysis of RCTs failed to show a survival benefit with GDT,[7] although GDT effectively reduced mortality in sepsis patients according to the meta-analysis published prior to the recent large multicenter trials.[6]

There are several possible explanations as to why the clinical benefit of GDT is diminishing in the more recent trials. As we observed in the present analysis, the amount of fluid administration (Table 3) between standard-care and GDT groups in the most recent RCT[5] (study period: 2011–2014) was not significantly different, compared with other two prior RCTs (Table 3). Since GDT was integrated into the SSC guidelines, it has been widely adopted as a part of sepsis care, and healthcare professionals involved in the recent trials were very familiar with GDT practices. We surmise that this is why the amount of fluid was not different between the standard-care and GDT groups with the passage of time.

We also noted the issue of the time of study enrollment, which is the reason why we conducted a cumulative meta-analysis to assess the time-dependent changes in risk reduction of GDT in sepsis patients. Subgroup analysis according to the actual period of the trial enrollment was performed. There are always time intervals between the year of enrollment and study publication; a clinical trial of patients with septic shock is extensive and can span many years. The actual clinical practices in the field are always changing; therefore, methods in more recent publications will differ from those of previous years. We assumed that the GDT protocol set in the year of the initiation of the trial reflected the skill and methodology trends of the clinical staff in that particular year. Hence, in addition to our main analysis, we arranged the trials chronologically according to the year of initiation of study enrollment and performed a cumulative analysis (Fig. 5), which showed that the 95% CIs of the ORs were surpassed as more recent trials were included. The comparison of the amount of fluid administration in Table 3 also indicates that the usual care is changing. The fluid management of usual care seems to be becoming similar to the fluid administration of GDT. However, we cannot hastily conclude that usual care is identical to GDT care based on this data alone.

A limitation of our study was that we included RCTs and non-RCTs together. We therefore could not dismiss the heterogeneity of this study. In Table 2, the overall I^2 value was 57.71% for all trials, which suggests that there is heterogeneity amongst the included trials; therefore, it cannot be ruled out that heterogeneity may have affected the results of the analysis. In critical care settings, it is extremely difficult to perform randomized studies; hence, there are numerous prospective observational studies evaluating the effectiveness of GDT.

Additionally, as we aimed to investigate the effectiveness of GDT, the treatment duration goal was heterogeneous. In a subgroup analysis that includes the initiation of the study enrollment, the year cannot reflect the entire eligibility period of a trial. Even during study enrollment, the clinical performance of the medical staff can progress, regress, or change. When arranging the trials chronologically according to the initiation year, such performance changes were not taken into account.

In summary, this meta-analysis suggests that GDT reduces mortality in patients with severe sepsis or septic shock. However, a cumulative meta-analysis revealed that the effect of risk reduction decreased as more recent studies were incorporated. Additional investigation is required prior to making definitive recommendations with respect to the effect of GDT on the resuscitation of patients with sepsis.

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