Systematic Review

Early goal-directed therapy reduces mortality in adult patients with severe sepsis and septic shock: Systematic review and meta-analysis

Legese Chelkeba[1, 2, 3,4], Arezoo Ahmadi[2], Mohammad Abdollahi[3], Atabak Najafi[2], Mojtaba Mojtahedzadeh[1, 2,3]

Abstract

Introduction: Survival sepsis campaign guidelines have promoted early goal-directed therapy (EGDT) as a means for reduction of mortality. On the other hand, there were conflicting results coming out of recently published meta-analyses on mortality benefits of EGDT in patients with severe sepsis and septic shock. On top of that, the findings of three recently done randomized clinical trials (RCTs) showed no survival benefit by employing EGDT compared to usual care. Therefore, we aimed to do a meta-analysis to evaluate the effect of EGDT on mortality in severe sepsis and septic shock patients. **Methodology:** We included RCTs that compared EGDT with usual care in our meta-analysis. We searched in Hinari, PubMed, EMBASE, and Cochrane central register of controlled trials electronic databases and other articles manually from lists of references of extracted articles. Our primary end point was overall mortality. **Results:** A total of nine trails comprising 4783 patients included in our analysis. We found that EGDT significantly reduced mortality in a random-effect model (RR, 0.86; 95% confidence interval [CI], 0.72–0.94; $P = 0.008$; $I^2 = 50\%$). We also did subgroup analysis stratifying the studies by the socioeconomic status of the country where studies were conducted, risk of bias, the number of sites where the trials were conducted, setting of trials, publication year, and sample size. Accordingly, trials carried out in low to middle economic income countries (RR, 0.078; 95% CI, 0.67–0.91; $P = 0.002$; $I^2 = 34\%$) significantly reduced mortality compared to those in higher income countries (RR, 0.93; 95% CI, 0.33–1.06; $P = 0.28$; $I^2 = 29\%$). On the other hand, patients receiving EGDT had longer length of hospital stay compared to the usual care (mean difference, 0.49; 95% CI, –0.04–1.02; $P = 0.07$; $I^2 = 0\%$). **Conclusion:** The result of our study showed that EGDT significantly reduced mortality in patients with severe sepsis and septic shock. Paradoxically, EGDT increased the length of hospital stay compared to usual routine care.

Keywords: Duration of mechanical ventilation, duration of vasopressor therapy, early goal-directed therapy, length of hospital stay, length of Intensive Care Unit stay, overall mortality, sepsis, septic shock, severe sepsis

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Introduction

Severe sepsis and septic shock are common with an annual incidence of 300/100,000/year in United States.[1] Despite an improvement in health care technologies and services, sepsis syndrome remains to be a condition with high mortality (20–50%).[1-3] Even though there is scarcity of studies on the long–term outcomes, few evidences showed that severe sepsis and septic shock affect a vast array of quality of life.[4,5] It has been shown that the progression of sepsis is time dependent and deserves here to be called "time is life" and when one considers its number of organs failed and mortality, it makes sense to treat the patients emergently and institute therapies that can prevent the progression of organs failure and improve outcomes in a time sensitive fashion.[1]

One of the breakthroughs in the 21 century about sepsis and its management was the work is done by Rivers *et al*., the so called "early goal-directed therapy (EGDT)."[6] The study focused on timely assessment and treatment. The protocol for EGDT called for central venous catheterization to monitor central venous pressure (CVP) and central venous oxygen saturation ($SCVO_2$), which is used to guide the use of intravenous fluids, vasopressors, packed red-cell transfusions and dobutamine in order to achieve prespecified physiological targets. The survival sepsis campaign (SSC)[7] recommendations were based on this single centered study and criticized by a number of expertise and scholars. Despite the absolute reduction of 16% in mortality reported by Rivers *et al*.,[6] a number of questions raised whether all elements of the protocol were necessary or not.[8-15] As a matter of fact, the applicability of this protocol is in question because it did not take into account the poor people, especially people living in developing countries where even basic health care services are not available leave alone such aggressive, resource consuming treatment.[16]

Nevertheless, a recent meta-analysis was done by Gu *et al*. up on pooling data from 13 showed that EGDT reduced mortality in the random-effects model (relative risk [RR], 0.83; 95% confidence interval [CI], 0.71−0.96; $P = 0.01$; $I^2 = 56\%$).[17] The beginning of the concept of EGDT was in 2001, but GU *et al*. included data before this time which might not include all components of the EGDT or the time of goal-directed therapy was unclear. Besides, our study included three new trials that have been done after the meta-analysis by GU *et al*.[17] and we hoped that a new meta-analysis included these trials with increased study population size may guide us better on EGDT in severe sepsis and septic shock. Another two very recent meta-analyses were published after we finalized the analysis and made ready for publication of this study.[13,14] According to the results of these studies, EGDT was not associated with a survival benefit among patients with severe sepsis or septic shock. We planned to analyze different aspects of EGDT versus usual care stratifying the studies according to socioeconomic status, the risk of bias, the number of sites, settings, publication year, and sample size. We also included some other outcome measures such as length of hospital stay, length of Intensive Care Unit (ICU) stay, duration of mechanical ventilation, and vasopressor therapy, which in turn may have important implications on health care resource consumption. Therefore, we believe that including trials after Rivers *et al*. work enable us to obtain better clarity and further answers for questions like "is earlier is the better?"

Methodology

Search strategy

Two investigators (LCH and AA) independently searched electronic databases in Hinari, PubMed, EMBASE, and the Cochrane database from 2001 to March 2015 using the terms "Early goal oriented therapy," "protocolized therapy," "modified therapy" or " EGDT," combined with the terms "septicemia" or "sepsis" or "severe sepsis" or "septic shock" in duplicate. A manual search for additional relevant studies using references from retrieved articles was also performed. Conference abstracts and unpublished studies were excluded. We restricted the searches to human studies with no language restriction placed on the searches. The meta-analysis reported in accordance with the PRISMA guideline.[18] Endnote ×6 was used to maintain and manage our library.

Types of studies, participants, and interventions

We included all randomized clinical trials (RCTs) involving EGDT in which treatment accomplished within the first 6 h of diagnosis of sepsis versus usual care. We included trials on adult patients with sepsis, severe sepsis, and septic shock. We excluded studies on neonates; patients aged less 18 years and pregnant women. The intervention had to be EGDT, which involved protocol based use of hemodynamic monitoring and manipulation of hemodynamic parameters to achieve predetermined hemodynamic endpoints compared to usual care in which all aspects of therapy was based on the desertion of the clinicians care for the patients.

Outcome measures

The primary outcome was the overall mortality. We considered overall mortality if the time reported was the longest time reported on the trial. For instance if a trial reported 28, 60, and 90 days of mortality, we took 90-day of mortality as overall mortality (our primary outcome) and so on. When it was not reported, we contacted the authors, and if they did not respond or told us that

the required data were not available, we excluded the trial(s) from the analysis. Other secondary outcomes considered in this meta-analysis were the length of stay in an ICU, length of hospital stay, duration of mechanical ventilation, and duration of vasopressor therapy.

Data abstraction

Two independent authors (LCH and AA) extracted data from all eligible studies on to a standardized data abstraction sheet. The extraction was checked by another author independent of the data extraction, who was also our monitor with long year of experiences of caring for septic patients and did a number of controlled RCTs on septic patients (MM). We extracted information on study author, year of publication, country, sample size included in EGDT and usual care, clinical settings, time of initiation of therapy after diagnosis of sepsis, primary (overall mortality), and secondary endpoints. E-mails were sent to the corresponding or first author of the studies or abstracts for missing information and waiting time of 4–6 weeks was taken for the response except ProMISe study, which we could not contact the authors for information, we could not understand such as duration of mechanical ventilation and vasopressor therapy due to shortage of time. If there were no responses, we excluded the study or the parameter that was not available.

Assessment of risk of bias in included studies

Two review authors (LCH and AA) independently assessed the included trials for bias according to the methods described Cochrane Handbook for Systematic Reviews of Interventions.[19] The following parameters were assessed: Sequence generation, allocation concealment, masking (blinding) of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting. Other sources of bias were a risk of bias related to the specific study design used or trial stopped early due to some data-dependent process or an extreme baseline imbalance in patients selected according to this hand book. Publication bias was analyzed once sufficient RCTs were identified by visual inspection of asymmetry in funnel plots, as well as the Egger's test. $P < 0.05$ considered as statistically significant.

Measures of treatment effects

We followed the Cochrane hand book of data analysis and reported dichotomous outcome measures to assess the summary effects of treatment by calculated risk ratio (RR) with (95%, CI) and continuous outcomes as calculated weight mean difference (MD). Preplanned subgroup analysis was also conducted to see whether there was a change in the mortality rate. We did a sensitivity analysis by sequentially deleting a single study each time in an attempt to identify the potential influence of an individual study and stability of the result.

Assessment of heterogeneity and data synthesis

After detail examination of the study by the investigators, we tested for statistical heterogeneity between the trails using I^2 and considered value >60%; and $P < 0.05$ as substantial heterogeneity. A random-effect model was used to estimate the overall treatment effects, and we reported $P < 0.05$ as statistically significant. The analyses were carried out using Rev Man 5.3 software (The Nordic Cochrane Center, Denmark) to create a summary findings table.

Results

Literature searches and selection

In the initial research, we found 1352 records in electronic search databases such as Hinari, PubMed, EMBASE, Cochrane, and 6 with hand searching from other sources, from which 1221 records remained after removing duplication. After examination and screening for the titles and abstracts, 1172 records were excluded. We assessed the full texts of 49 remained records for eligibility, and 40 records were further excluded for not fulfilling the inclusion criteria. Finally, 9 controlled randomized trials were included in analyses[6,11-13,16,20-23] as described in Figure 1.

Study characteristics

We included trials published between 2001 and March 2015. The sample size of the trials ranged from 33 to 1581 with a total number of 4787, of which 2384 were assigned to the EGDT and 2403 to usual care. There were two studies from USA,[6,11] 3 from China,[20,21,23] 1 from Taiwan,[22] 1 from Zambia,[16] 1 from UK,[13] 1 from Australia, and New Zealand.[12] Four trials were conducted in ICU,[20-23] whereas the remaining five[6,11-13,16] studies in the emergency department. Three studies were multicenter RCTs[11-13] and six studies were single center studies.[6,16,20-23] Three trials were published in The Chinese language[20,21,23] and the remaining six trials were in English.[6,11-13,16,22] Early resuscitation within 6 h of sepsis diagnosis was reported in all studies.[6,11-13,16,20-23] Three trials reported the length of ICU stay,[11-13] four trials reported the length of hospital stay,[6,11-13] three trials reported the duration of mechanical ventilation and vasopressor therapy.[6,11,12] All studies included in this meta-analysis reported the baseline characteristics of the patients in between groups (EGDT and usual care) were homogenous. The characteristics of the RCT studies fulfilling the inclusion criteria are listed in Table 1.

Risk of bias in included trials

We used the Cochrane collaboration tool to assess the risk of bias of individual study and represented the detail

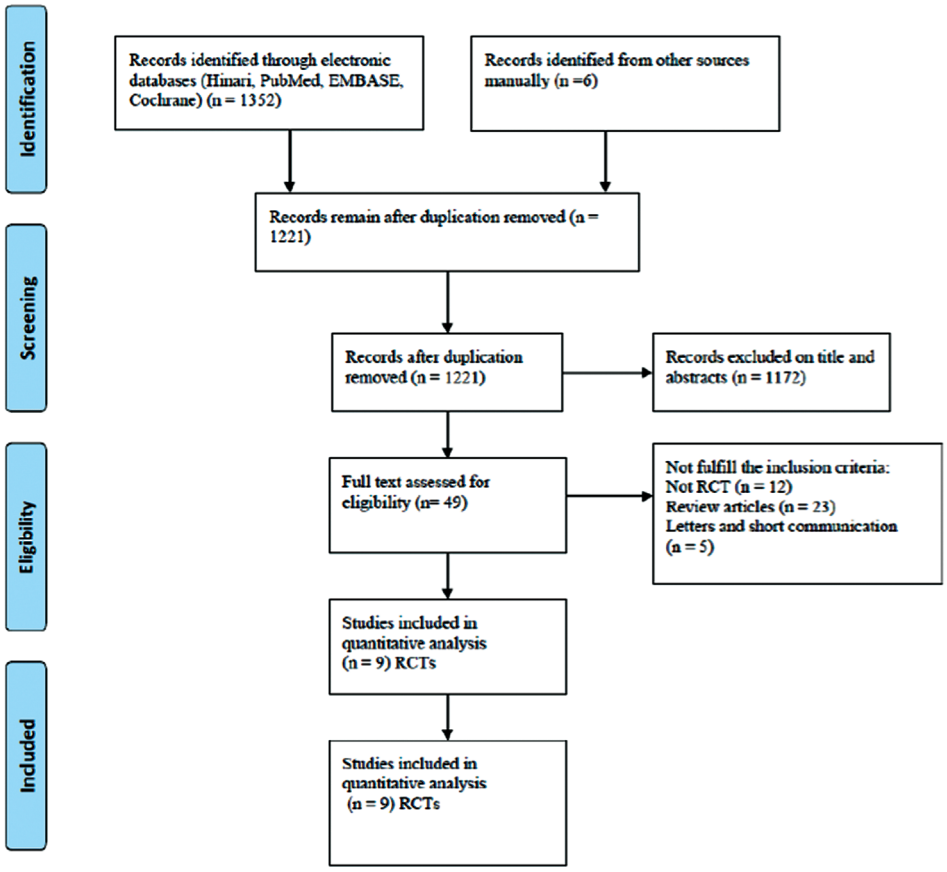

Figure 1: Flow chart of study design and patient selection

Table 1: Characteristics of included randomized control trials

Author Year, country	Sample size EGDT	Sample size Usual care	Setting	Time of initiation	Mortality	LICU*(day)	LHS (day)*	DMV (day)	DVPT (day)*
Andrews 2014 Zambia	53	56	ED SC	Within 6 hours	Hospital				
Lin 2006 Taiwan	108	116	ICU SC	Within 6 hours	Hospital				
ProCESS 2014 USA	439	902	ED MC	Within 6 hours	Hospital	EGDT: 5.1±6 UC: 4.7±5.8	EGDT: 11.1±10 UC: 11.3±10.9	EGDT: 6.4±8.4 UC: 6.9±8.2	EGDT: 2.6±1.6 UC: 2.5±1.6
He 2007, china	98	105	ICU SC	Within 6 hours	Hospital				
Yan 2010, china	159	148	ICU SC	Within 6 hours	ICU				
Wang 2006, china	16	17	ICU SC	Within 6 hours	14 day				
ARISE 2014, Australia and NewZealand	796	804	ED MC	Within 6 hours	90-day	EGDT: 3±3.7 UC: 3.2±4.3	EGDT: 9.5±11.9 UC: 9.6±11.9	EGDT: 82.4±163.4 UC: 78±137.2	EGDT: 33.2±48.3 UC: 37.4±53
Rivers *et al* 2001, USA	130	133	ED MC	Within 6 hours	Hospital		EGDT: 13.2±13 UC: 13.0±13.7	EGDT: 9.0±11.4 UC: 9.0±13.1	EGDT: 1.9±3.1 UC: 2.4±4.2
ProMISe, UK	630	630	ED MC	Within 6 hours	90- day	EGDT: 3±1.2 UC: 2.4±1.3	EGDT: 10.8±4.3 UC: 10±3.5		

*all data presented as mean±SD. Abbreviations: LICU: Length of ICU stay in days; LHS: Length of hospital stay in days; DMV: Duration on mechanical ventilation in days; DVT: Duration on vasopressor therapy in days; EGDT: Early goal directed therapy; UC: Usual care; ED: Emergency department; MC: Multicenter; SC: Single center

of the results in Figure 2. Six studies[6,11-13,16,22] were judged had a low risk of bias, whereas the remaining three[20,21,23] trials were at unclear risk of bias. The investigators of the trials clearly generated ample randomized sequences in seven trials,[6,11-13,16,21,22] and appropriate allocation concealment were reported in six[6,11-13,16,22] studies as

described in Figure 2. None of the these included nine trials were double blinded as it is difficult to blind the clinicians in such difficult situations, and we believe that such act did not influence the outcomes of interest.

Primary outcome: Overall mortality

Mortality data were available in all nine[6,11-13,16,20-23] studies included in the meta-analysis. The results of this study showed that the overall mortality rate in EGDT and usual care groups was 712 (29.7%) of 2384 and 812 (33.8%) of 2403, respectively, an absolute 4.1% (100 patients) risk reduction. Hence, EGDT significantly reduced overall mortality in the random-effect model (RR, 0.86; 95% CI, 0.76–0.96; $P = 0.008$; $I^2 = 50\%$) as shown in Figure 3. We also did preplanned subgroup analysis stratifying patients by the socioeconomic status of countries, the risk of bias, setting, sites of study, year of publication, and sample size. Accordingly, we found that studies carried out in low to middle income countries had lower overall mortality rate in random-effect model (RR, 0.78; 95% CI, 0.67–0.91; $P = 0.0.002$; $I^2 = 34\%$) compared to those studies in higher income countries (RR, 0.93; 95% CI, 0.83−1.06; $P = 0.28$; $I^2 = 29\%$) Figures 3-6. The result of other subgroups was displayed in Table 2.

Secondary outcomes: Measures of health care cost resource consumption

The results of four[6,11-13] aggregated trials in this study showed that patients assigned to EGDT had longer lengths of hospital stay compared to the usual care (MD, 0.49; 95% CI, −0.04−1.02; $P = 0.07$; $I^2 = 0\%$) as described in Figure 7. The results of the analyses of length of ICU stay (MD, 0.27; 95% CI, −0.33−0.87; $P = 0.38$; $I^2 = 86\%$) with substantial heterogeneity, duration of mechanical ventilation (MD, −0.04; 95% CI; −0.57−0.48; $P = 0.87$; $I^2 = 0\%$), and the duration of vasopressors therapy (MD, −0.09; 95% CI; −0.36−0.19; $P = 0.53$; $I^2 = 59\%$) showed that there was not statistical significant difference between EGDT and usual care as shown in Table 3.

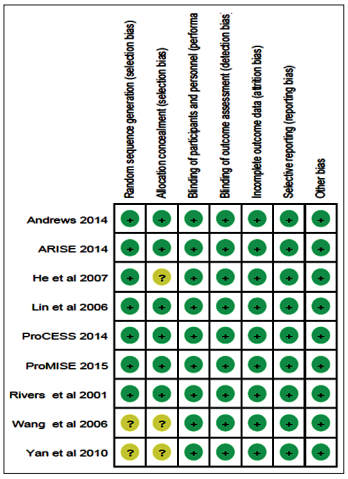

Figure 2: Risk of bias summary

Sensitivity analysis

Upon performing a sensitivity analysis for each outcome by removing a single study at a time to evaluate the stability of the results analysis, we obtained statistically similar results after omitting each of the studies [Table 4]. This indicated the good degree of stability in the findings of this meta-analysis.

Table 2: Subgroup analysis of overall mortality

Subgroup	#of studies	#patients	RR (95% CI)	*P* value	I^2 (%)
Overall mortality	9	4787	0.86 (0.76, 0.97)	0.008	50
Socioeconomic status					
High income	4	3911	0.93 (0.83, 1.06)	0.28	29
Low-middle income	5	876	0.78 (0.67, 0.91)	0.002	34
Risk of bias					
Low risk of bias	6	4244	0.89 (0.78, 1.02)	0.11	57
Unclear risk of bias	3	543	0.75 (0.63, 0.89)	0.001	0
Setting					
ICU	4	767	0.73 (0.63, 0.83)	<0.00001	0
ED	5	4020	0.95 (0.86, 1.05)	0.33	12
#Site of study					
Single centered	6	1139	0.77 (0.68, 0.88)	<0.00001	19
Multicenter	3	3648	0.98 (0.88, 1.10)	0.75	0
Publication year					
Before 2008	4	723	0.74 (0.64, 0.84)	<0.00001	0
After 2008	5	4064	0.94 (0.83, 1.06)	0.29	37
Sample size					
<500	6	1139	0.77 (0.68, 0.88)	<0.00001	19
>500	3	4648	0.98 (0.88, 1.10)	0.75	0

Abbreviations: RR: Risk ratio; ICU: Intensive care unit; ED: Emergency department

Table 3: Pooled analysis of secondary outcomes

Outcome measures	Number of studies	MD (95% CI)	*P*	I^2 (%)
Length of ICU stay (day)	4	0.27 (−0.33, 0.87)	0.38	86
Duration of mechanical ventilation (day)	3	−0.04 (−0.57, 0.48)	0.87	0
Duration of vasopressor therapy (day)	4	−0.09 (−0.36, 0.19)	0.53	59

Abbreviations: MD: Means difference; ICU: Intensive care unit

Table 4: Sensitivity analysis for overall mortality by omitting each study in random-effects model

Study omitted	RR (95% CI)	*P* value	I^2 (%)
Andrews *et al*. 2014	0.84 (0.74, 0.95)	0.005	52
ARISE 2014	0.84 (0.74, 0.97)	0.006	51
He *et al*. 2007	0.87 (0.76, 1.00)	0.02	55
Lin *et al*. 2006	0.89 (0.80, 1.00)	0.03	43
ProCESS 2014	0.84 (0.74, 0.96)	0.01	54
ProMISe 2015	0.83 (0.74, 0.94)	0.003	43
Rivers *et al*. 2001	0.87 (0.77, 0.98)	0.03	51
Wang *et al*. 2006	0.86 (0.76, 0.97)	0.01	56
Yan *et al*. 2010	0.88 (0.78, 0.99)	0.03	46

Abbreviations: RR: Risk ratio

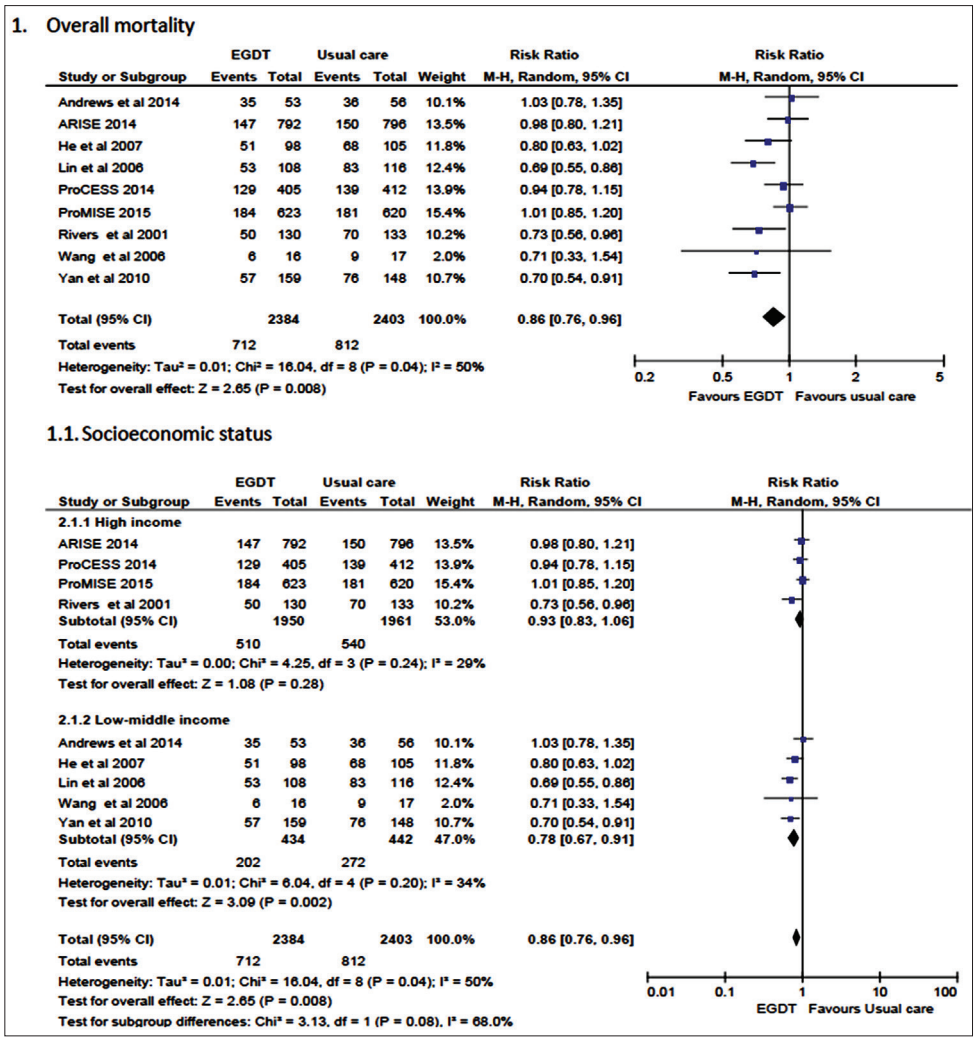

Figure 3: Forest plot of overall mortality. The study was stratified by socioeconomic status. Risk ratio (RR) < 1 favors EGDT. CI = confidence interval; M-H = Mantel-Haenszel

Publication bias

We assessed the funnel plot for asymmetry by visual inspection, in addition, to the statistical test by Egger test ($P = 0.36$) and found no publication bias [Figure 8].

Discussion

This meta-analysis primary dealt with the mortality benefits of EGDT severe sepsis and septic shock patients. It has been demonstrated that sepsis is a medical emergency and needs immediate attention.[1] Rivers *et al.* were the first to bring "EGDT" and it is survival benefits into attention.[6] The SSC guidelines also recommend the use of CVP at a target goal of 8–12 mmHg for nonintubated patients and 12–15 mmHg for intubated patients.[7] In addition, the target for mean arterial pressure should be greater or equal to 65 mmHg, urine output of greater or equal to 0.5 ml/kg/h for at least 2 h and $SCVO_2$ of ≥70% by the use of either packed red blood cells or dobutamine infusion. Accordingly, early resuscitation targeted to achieve and maintain these physiological variables within the first 6 h of shock improved survival. After the publication of that article by Rivers *et al.*,[6] there have been many changes in the management of sepsis, raising the question of whether all elements of the protocol are still necessary or not,[8-15] For instance, the normal $SCVO_2 \geq 70\%$ does not necessarily reflect adequate deliver oxygen as sepsis is a disease with derangement of oxygen extraction and utilization that lead to near normal or even supranormal $SCVO_2$ despite active tissue dysoxia.[24] In addition, there are some evidences showing the inferiority of static indices compared to dynamic indices in predicting the responsiveness of fluid therapy in patients with severe sepsis and septic shock questioning the importance of CVP.[25,26] Furthermore, the most recent largest trials[11-13] and meta-analyses[14,15] also concluded that there was no significant difference of mortality benefits between patients assigned to EGDT versus usual care. Moreover, the ProMISe study came up with the conclusion of EGDT increased costs of care.[13]

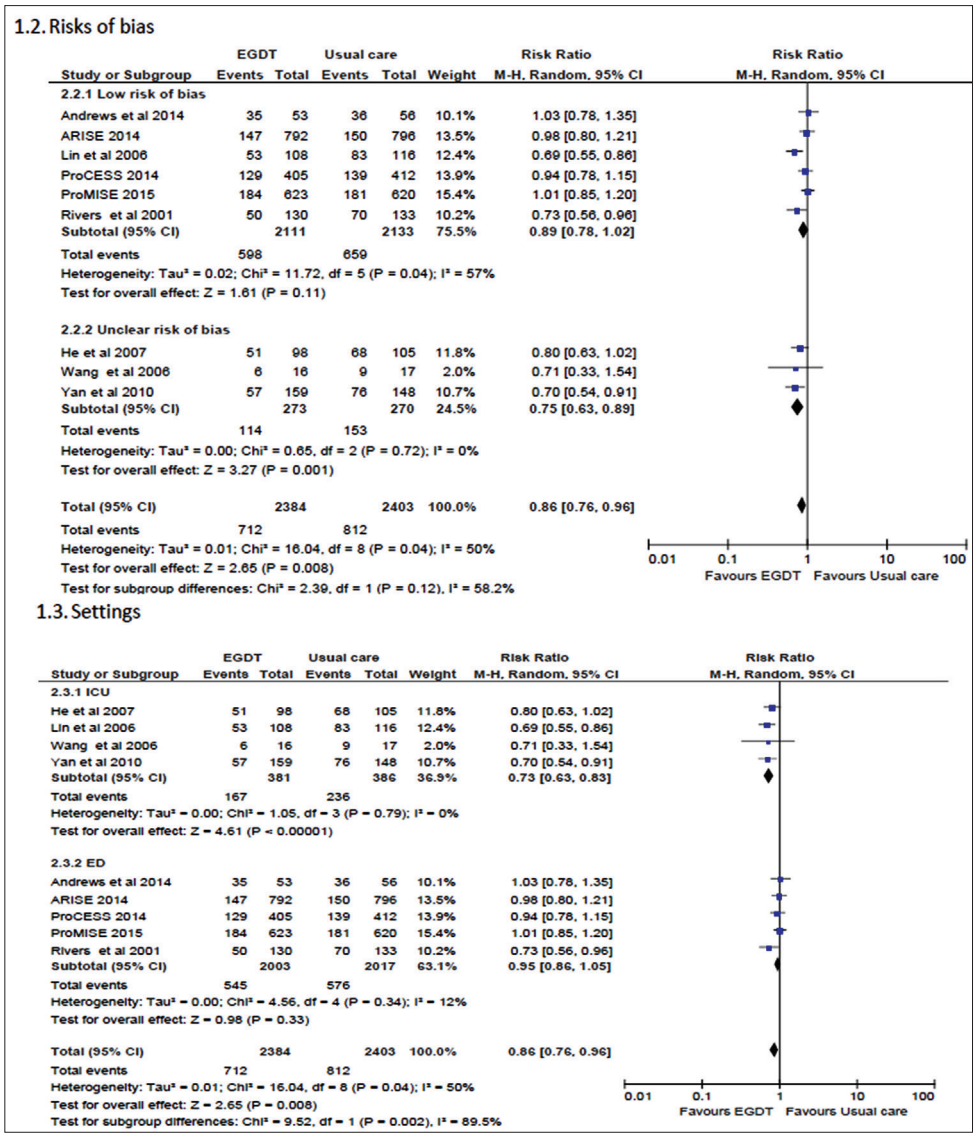

Figure 4: Forest plot of overall mortality. The study was stratified risk of bias and settings where study carried out. Risk ratio (RR) <1 favors EGDT. CI = confidence interval; M-H = Mantel-Haenszel.

On the other hand, two meta-analyses were done by Wira *et al*.[27] that included all protocolized goal-directed hemodynamic optimization for the management of severe sepsis and septic shock in the emergency departments and Gu *et al*.[17] included RCTs involving goal-directed therapy in patients with sepsis pointed out that EGDT significantly reduced mortality.

Because of the conflicting conclusions made by the after mentioned trials and meta-analyses, we aimed to evaluate the benefits of EGDT compared to the usual routine care by including 9 RCTs conducted since the work of Rivers *et al*. According to our study, EGDT reduced mortality significantly by 14% (RR, 0.86; 95% CI, 0.76−0.96; $P = 0.008$; $I^2 = 50\%$). The study also showed that EGDT increased the length of hospital stay (MD, 0.49; 95% CI, −0.04−1.02; $P = 0.07$; $I^2 = 16\%$) compared to the usual care. This increased length of hospital stay has an important implication of resource consumption in the hospital. On the other hand, EGDT had no significant effect on length of ICU stay, duration mechanical of ventilation, and duration of vasopressor therapy.

Comparing our study with 4 recently done meta-analyses, survival benefits were observed on two of them[17,27] and negative in other two.[14,15] The disagreement between these studies could be explained as follows. First, the Wira *et al*.[27] reported that EGDT improved survival by including fifteen studies of which only one was RCT. By including only one RCT and 14 observational studies, there was a high likelihood of risk of bias. Second, the study conducted by GU *et al*.[17] included studies that were not goal-directed (did not include SVO_2 monitoring), nonrandomized and one study that included nonsevere

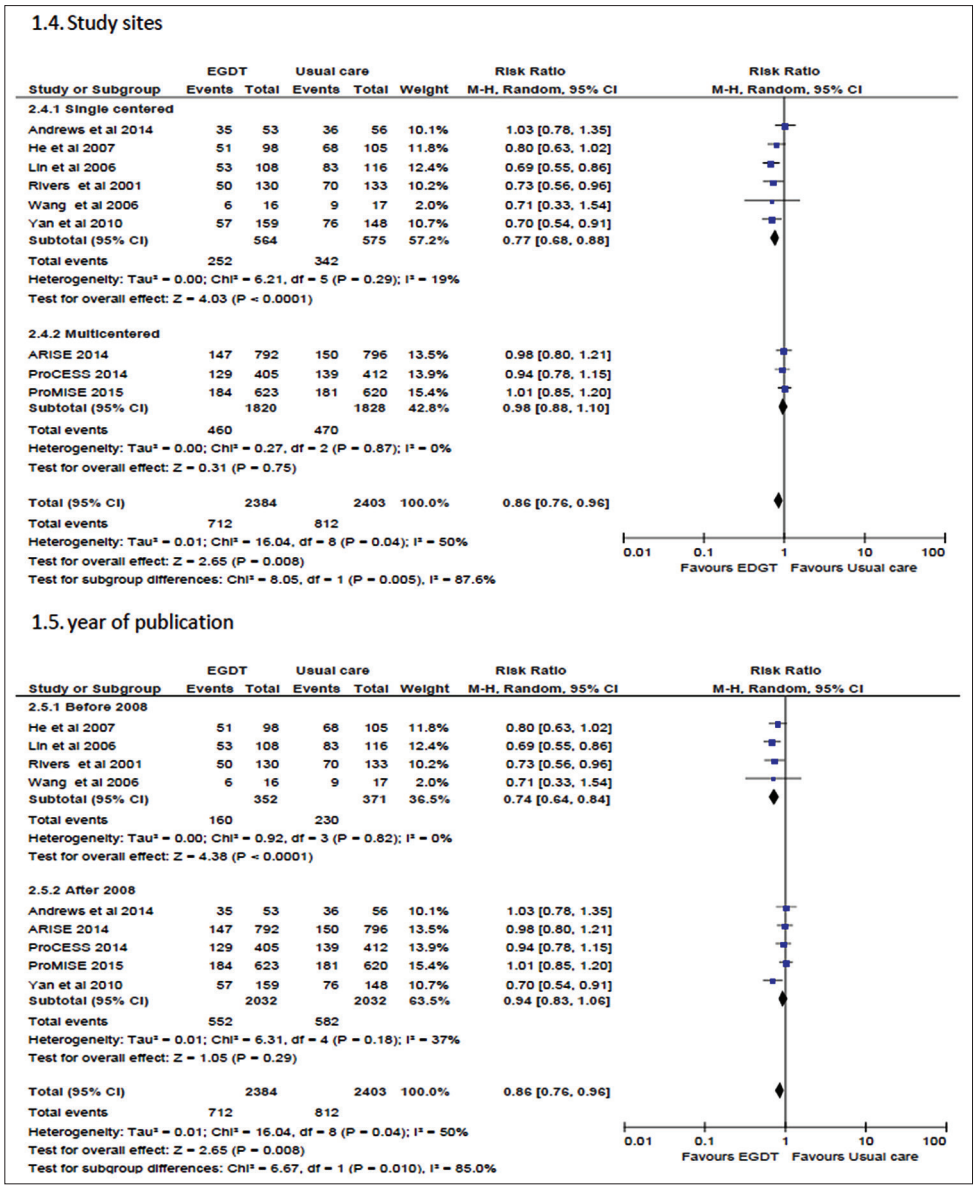

Figure 5: Forest plot of overall mortality. The study was stratified by number of sites, publication year. Risk ratio (RR) <1 favors EGDT. CI = confidence interval; M-H = Mantel-Haenszel

sepsis and septic shock patients. Third, the work by Zhang *et al*.[15] did not include the ProMISe study, one of the largest harmonized trials currently we have. Finally, Angus *et al*.[14] reported that there was no mortality benefit by employing EGDT. However, the primary focus of this study was on those studies with large sample size and done at the emergency department, perhaps undermining the survival benefits of EGDT in ICU shown by our study. Comparison of prior meta-analyses with the current study was shown in Table 5.

What does our study add to the current literature then?

Our study included RCTs performed in the different

Table 5: Comparison of this study with four recently done meta-analyses

Features	Our study	Wira	GU	Zhang	Angus
Year of searching	2001-2015	1980-2011	Inception-2014	2001-2014	2000-2015
#of studies included	9	15	13	10	11
RCT	9	1	13	10	11
Findings Survival benefits	EDGT Positive	EGDT Positive	GDT Positive	EGDT Negative	EGDT Negative
Journal of publication	Not yet	Western Journal of Emergency Medicine	Critical care	BMC medicine	Intensive care medicine

Abbreviation: RCT: Randomized clinical trial; EGDT: Early goal directed therapy; GDT: Goal directed therapy

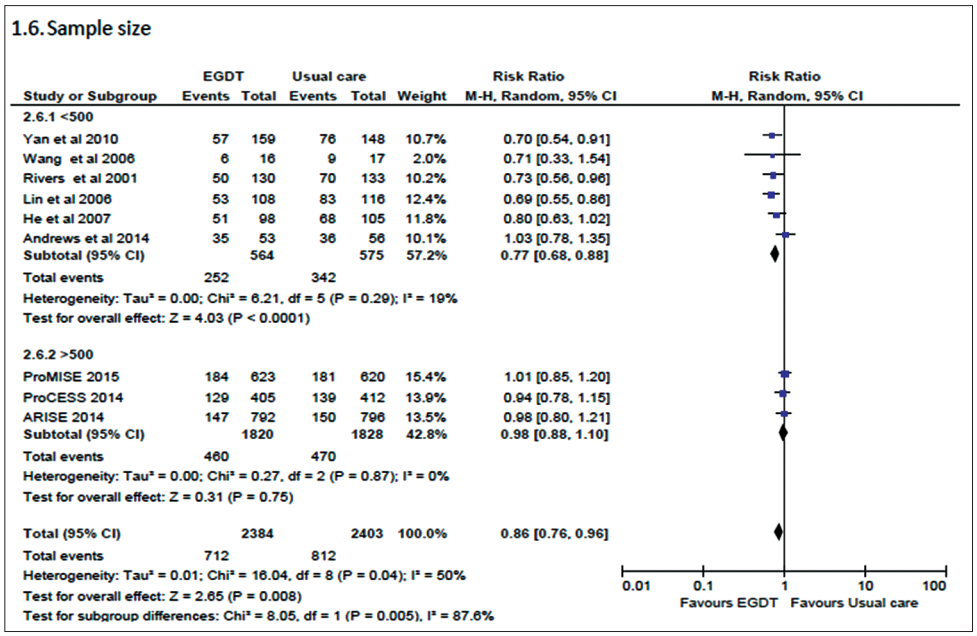

Figure 6: Forest plot of overall mortality. The study was stratified by number of sites, publication year. Risk ratio (RR) < 1 favors EGDT. CI = confidence interval; M-H = Mantel-Haenszel

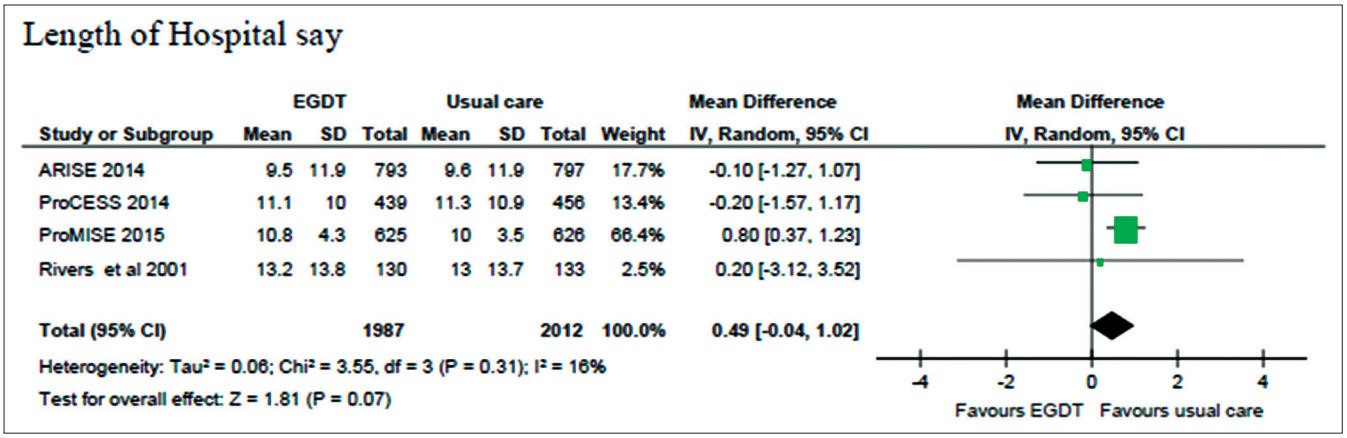

Figure 7: Forest plot of Lengths of Hospital say. Mean weight difference (MWD) < 0 favors EGDT. CI = confidence interval, IV = inverse variance

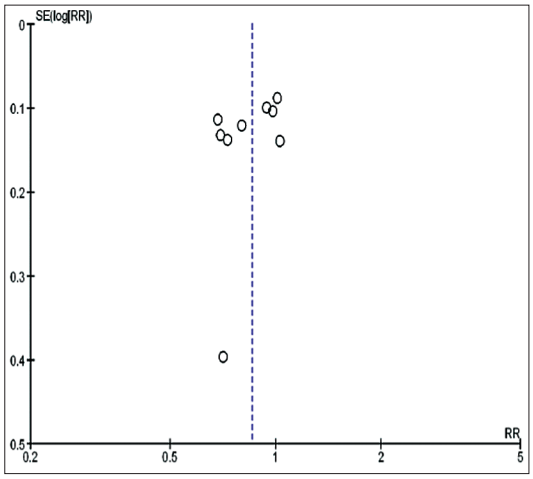

Figure 8: The funnel plot of overall mortality

geographical area of the world; Asia, Africa, Europe, and North America with a large sample size that can detect a significant difference between the study groups. We also include the three rigorous largest trails we have to date; the ProCESS, ARISE, and ProMISe. Of all, we did *post-hoc* subgroup analyses by stratifying trials into those in developing countries and developed countries depending on their socioeconomic status, the risk of bias, settings, sites, year of publication and sample size. The results of these subgroup analyses showed that there was statistically significant reduction in mortality in low to middle income countries, with unclear risk of bias, done in ICU, single centered, those published before 2008 and those with sample size <500. This looks

paradoxical. Because it is ridiculous to extrapolate the results of developed nations to that of developing countries as they have different capability and capacity, we suggest an adequately powered, randomized, placebo-controlled trial of high methodological value from both developing and developed countries or parallel studies in both areas and compare the results head to head. Another important issue here is that SSC guidelines were formulated in 2004[28] and reevaluated in 2008.[29] The result of the current study showed that those studies before 2008 significantly reduced mortality compared to those after 2008. This in turn questioned the continuous application of SSC guidelines in real practice at this time. We also found across four studies presenting to the ED with severe sepsis and septic shock, EGDT was not associated with reduced mortality compared with usual care; a result similar to Angus *et al*.[14] However, in studies involved patients admitted to ICU, EGDT significantly reduced mortality and this is in line with a study by Gu *et al*.[17] This is also an issue deserve mentioning since all currently available studies involving ICU patients were conducted in a single center, and this needs validation by doing multicenter RCT.

Our study has a number of limitations that we should be careful when interpreting the findings. First we included only 9 RCTs, although our sample size is large enough. Second, the overall mortality was not similar across the studies included. Some of them reported 90-day mortality, in hospital mortality, ICU mortality, and even 14-day mortality. This variation in primary end points could modify the absolute risk. Third, the target goals for some of the studies we included were different, and the mortality difference might be due to these differences (for example, some of them used $SCVO_2$ and others did not).

Conclusion

Our study indicated that EGDT resulted in significant reduction of overall mortality compared to usual care in patients with severe sepsis and septic shock. The subgroup analysis, which in fact should be validated by well designed trail, showed that EGDT was significantly reduced mortality in trials done in low to middle income countries, with unclear risk of bias, done in ICU, single centered, published before 2008 and with sample size <500. We also observed that EGDT increased the length of hospital stay with no significant effect on length of ICU stay, duration of mechanical ventilation and duration of vasopressor therapy.

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Conflicts of interest

There are no conflicts of interest.

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