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Effect of Anticoagulant Versus Non-Anticoagulant Therapy on Mortality of Sepsis-Induced Disseminated Intravascular Coagulation: A Systematic Review and Meta-Analysis

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Abstract

Background: Sepsis is a syndrome of severe systemic inflammatory response. When combined with disseminated intravascular coagulation, mortality is increased. The need for anticoagulant therapy is still the focus of debate.

Methods: PubMed, Embase, Cochrane Library, and Web of Science were searched. Adult patients with sepsis-induced disseminated intravascular coagulation were included in this study. All-cause mortality as efficacy and serious bleeding complications as adverse effect were measured as primary outcomes. Methodological quality of included studies were assessed using the Methodological Index for Non-randomized Studies (MINORS). Meta-analysis was performed using R software (version 3.5.1) and Review Manager (version 5.3.5).

Results: There were nine eligible studies with 17,968 patients included. There were no significant reductions in mortality between the anticoagulant group and the non-anticoagulant group (RR, 0.89; 95% CI, 0.72–1.10; $P = 0.27$). The DIC resolution rate in the anticoagulation group has a statistically significant increase compared with the control group [OR: 2.62, 95% CI (1.54–4.45), $P < 0.05$]. And there was no significant difference in bleeding complications between the two groups (RR, 1.27; 95% CI, 0.77–2.09; $P = 0.69$). SOFA score reduction did not change significantly between the two groups ($P = 0.13$).

Conclusions: Our study observed no significant benefit of anticoagulant therapy on mortality of sepsis-induced DIC. Anticoagulation therapy can promote DIC resolution in sepsis-induced DIC. In addition, anticoagulant therapy does not increase the risk of bleeding in these patients.

Keywords

anticoagulant, mortality, sepsis-induced disseminated intravascular coagulation

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Introduction

Sepsis is a syndrome of severe systemic inflammatory response caused by the invasion of pathogenic microorganisms such as bacteria.[1] About 50% to 70% of patients with sepsis develop coagulation dysfunction, and about 35% of patients have significant disseminated intravascular coagulation (DIC), which is characterized by progressive progression from mild coagulation dysfunction to significant prothrombin time and partial thrombin activation time.[2] With the development of DIC, it causes microvascular thrombosis, hypoperfusion, organ dysfunction, and other injuries. Patients may be complicated with bleeding, which can easily lead to multiple organ dysfunction. This result in increased mortality, poor prognosis, and quality of life during treatment.[3]

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With the development of sepsis, exogenous and endogenous coagulation pathways can be activated simultaneously. Currently, there is no specific and feasible treatment that can improve the prognosis of patients with sepsis-induced DIC by blocking systemic inflammatory reaction or activating the blood coagulation system. In addition, the latest Surviving Sepsis Campaign guidelines (international guidelines for management of sepsis and septic shock) do not recommend routine anticoagulant therapy for sepsis patients.[4] Lyons *et al.*[5] found that the in-hospital mortality of patients without sepsis-associated coagulopathy was 25.4%, and that of patients with severe sepsis-associated coagulopathy was 56.1%. In addition, Kaplan–Meier curve showed an increasing trend of mortality from patients with mild sepsis-associated coagulopathy to those with severe sepsis-associated coagulopathy. Thus, early intervention may improve outcomes. At present, antithrombin, thromboregulatory protein, and protein C are the main anticoagulants.[6] In the Japanese clinical practice guidelines for management of sepsis and septic shock 2016 (J-SSCG2016),[7] the use of thrombomodulin in sepsis-induced DIC is not explicitly recommended. However, International Society on Thrombosis and Haemostasis (ISTH) recommends the use of thrombomodulin in patients with DIC.[8]

Therefore, whether anticoagulant therapy is necessary for sepsis-induced DIC patients is still the focus of current debate. In order to evaluate the effect of anticoagulation or non-anticoagulation on the prognosis of patients with sepsis-induced DIC, we conducted a systematic review and meta-analysis.

Method

This systematic review and meta-analysis are conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA 2020) Statament.[9] The study protocol was registered with International Prospective Register of Systematic Reviews (registration number: CRD42022382608). Ethical approval is not required in that this is a review of published studies.

Search Strategy

We performed comprehensive search on PubMed, Embase, Cochrane Library, and Web of Science databases, from database inception to November 2022, using the MeSH terms: 'anticoagulants', 'disseminated intravascular coagulation' and 'sepsis'. The MeSH terms and entry terms from PubMed were also used in the search of Embase, Cochrane Library, and Web of Science. The search items were designed based on the combination of MeSH terms and entry terms. The author information and reference lists of retrieved articles were searched for more study information.

Study Selection

Studies meeting the following criteria would be included: (i) study types: randomized control trials (RCTs) and observational studies (prospective/retrospective cohort studies with concurrent controls, cohort studies with historical controls), (ii) population: adult patients (age > 18 years) with sepsis-induced DIC, (iii) intervention: anticoagulants administration at any dose, (iv) control: placebo or no intervention (non-anticoagulants administration), and (v) outcomes: at least one of the following outcome measures: all-cause mortality, or intensive care unit or in-hospital mortality.

Studies with the following characteristics were excluded: (i) repeated publication, (ii) full text unavailable, (iii) studies that no data was available, (iv) sample size less than 5, and (v) the following article styles: review articles, letters, case reports, conference abstracts, editorials, and comments.

Study Quality

Methodological quality of included studies was assessed using the Methodological Index for Non-randomized Studies (MINORS).[10] And the process was conducted by two reviewers independently. MINORS has 12 items, and each item can be scored from 0 to 2 indicating on report, incomplete report, and sufficient report, respectively. The specific MINORS items are as follows: (i) a stated aim of the study, (ii) inclusion of consecutive patients, (iii) prospective collection of data, (iv) endpoint appropriate to the study aim, (v) unbiased evaluation of endpoints, (vi) follow-up period appropriate to the major endpoint, (vii) loss to follow-up not exceeding 5%, and (viii) prospective calculation of the sample size. The latter four items are designed for studies that have a control group, which are (i) a control group having the gold standard intervention, (ii) contemporary groups, (iii) baseline equivalence of groups, and (iv) statistical analyses adapted to the study design. In this meta-analysis, non-comparative studies scored for less than 8, within 9 to 12, and over 13 would be considered of low, medium, and high quality, respectively. Comparative studies scored for less than 12, within 13 to 18, and over 19 would be considered of low, medium, and high quality, respectively.

Data Collection

All criteria and data were defined before the study screening and data collection. Data collection was conducted by two reviewers independently. Any discrepancy would be settled by the third reviewer. For study screening, the article type, title, and abstract were assessed first. Then the full texts of the studies passed initial screening were reviewed for the final exclusion. The data included origin of the article, nationality, study type, inclusion and exclusion criteria, information relevant to the quality of the study, baseline data of patients, sepsis-induced DIC relevant data, and information relevant after using anticoagulant or non-anticoagulant.

Statistical Analysis

All data analyses were performed using R software (version 3.5.1, The R Foundation for Statistical Computing, Austria, Vienna) and Review Manager Version 5.3.5 (RevMan; The Cochrane Collaboration 2021, The Nordic Cochrane Centre, Copenhagen, Denmark). For categorical variables, the incidence

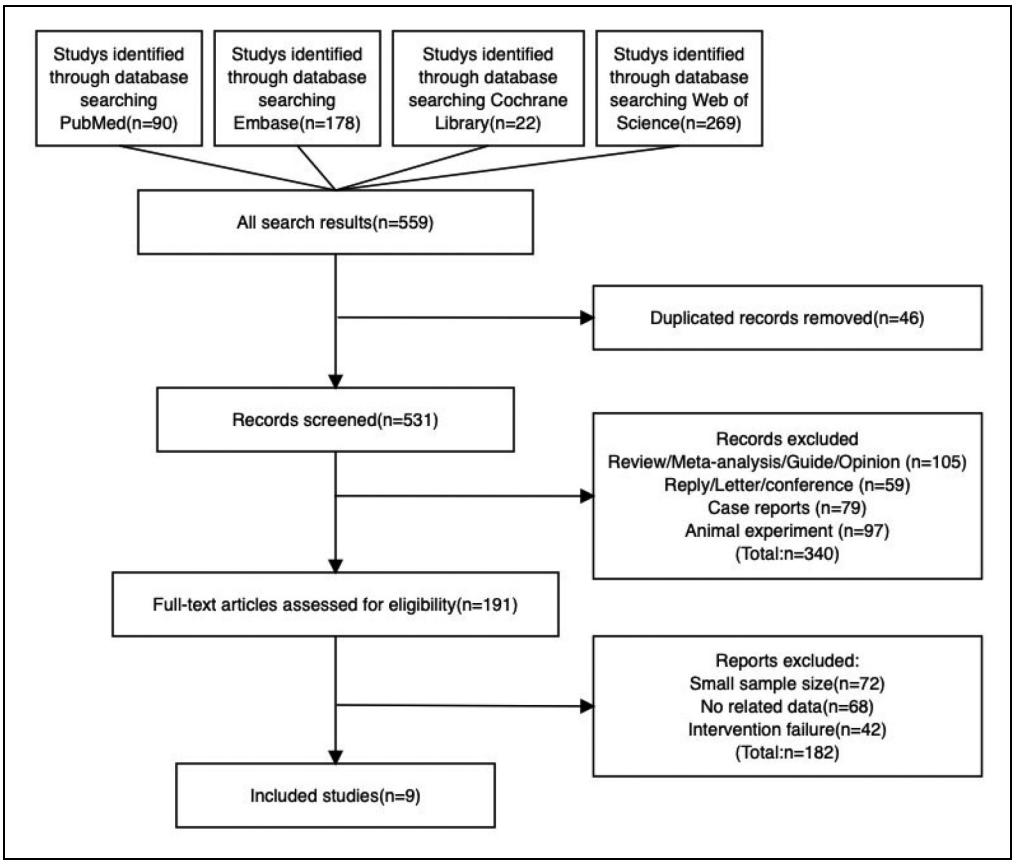

Figure 1. The study inclusion flow chart.

was calculated by dividing the number of total patients by the number of observed events. For continuous variables, median (IQR interquartile range) was converted to mean ± SD (standard deviation). Fixed-effect model and random-effect model were applied for meta-analysis to pool the effect size (ES) and 95% confidence interval (95%CI). Heterogeneity among included studies was assessed using I^2 statistic. An $I^2 < 25\%$ indicates low heterogeneity, $25\% < I^2 < 50\%$ indicates medium heterogeneity, and an $I^2 > 50\%$ indicates significant heterogeneity. Random-effect model would be applied if $I^2 > 50\%$, otherwise, fixed-effect model would be used.[11] If necessary sensitivity analysis would be conducted to assess the effect of individual study on the pooled size. Publication bias was assessed using funnel plot, Egger's test and Begg's test. Descriptive statistics was applied to analyze characteristics of the participants. A P value less than 0.05 indicated statistical significance.

Results

Selection of Studies

The study inclusion flow chart is shown in Figure 1. There were 559 relevant articles searched: 90 from PubMed, 178 from Embase, 22 from Cochrane Library, and 269 from Web of Science. These articles were screened according to the inclusion and exclusion criteria. Of the identified references, 46 and 340 were excluded because of duplications and article types, respectively. Additionally, there were 72 studies of small sample size, 68 studies without related data, and 42 studies of intervention failure removed. Finally, nine studies with 17,968 patients were included in this systematic review.[12–20]

Description of the Included Studies and Patients

The characteristics of the nine included studies are shown in Table 1. Publication date of these studies ranged from 2004 to 2022. All included studies were observational design, with three prospective studies and six retrospective studies.

Baseline characteristics of the patients are shown in Table 2. A total of 17,968 patients enrolled in the included studies. The primary tool these studies applied for sepsis and DIC severity assessment was Acute Physiology and Chronic Health Evaluation (APACHE-II), Child-Pugh score, Sequential Organ Failure Assessment (SOFA), Japanese Association for Acute Medicine (JAAM), and International Society on Thrombosis and Haemostasis (ISTH) were applied to assess the severity of critical patients.

Quality Evaluation

The results of the quality assessment using MINORS, and these scores are shown in Table 3. According to different grading standards, six studies were graded as low risk of bias and the

Table 1. Characteristics of Included Studies.

Study	Study timing	Anticoagulant type	Study subject	Inclusion criteria	Exclusion criteria
J.-F. DHAINAUT *et al*, 2004	NR	Drotrecogin alfa	Sepsis-induced DIC	Sepsis-induced DIC	NR
J.KIENAST *et al*, 2006	NR	AT	Sepsis-induced DIC	Sepsis-induced DIC	NR
Satoshi Gando *et al*, 2013	From April 2008 to February 2012	AT	Sepsis-induced DIC	DIC patients with sepsis and antithrombin levels of 50% to 80% ; JAAM DIC score≥4	less than 15 years of age;Liver cirrhosis classified as Child-Pugh grade C
Masafumi Yamato *et al*, 2013	From April 2009 to November 2012	rTM	Sepsis-induced DIC	Sepsis-induced DIC	NR
Jean-Louis Vincent *et al*, 2013	NR	ART-123	Sepsis-induced DIC	Sepsis-induced DIC	unable to obtain informed consent; presence of anydisorder other than sepsis that could alter coagulation
T.TAGAMI *et al*, 2014	From July 2010 to March 2013	AT	Sepsis-induced DIC	Sepsis-induced DIC	pregnancy; no administration of antibiotics
T. TAGAMI *et al*, 2015	From July 2010 to March 2013	rhTM	Sepsis-induced DIC	Sepsis-induced DIC	pregnancy; no administration of antibiotics
Akiyoshi Hagiwara *et al*, 2016	From August 2012 to July 2014	rhTM	Sepsis-induced DIC	Sepsis-induced DIC	refusal to participate; past history of hypersensitivity to rhTM
Takeshi Wada *et al*, 2022	From January 2016 to March 2017	AT and/or rhTM	Sepsis-induced DIC	Sepsis-induced DIC	missing data

Note: Not Reported, NR; disseminated intravascular coagulation, DIC; antithrombin, AT; recombinant thrombomodulin, ART-123; recombinant thrombomodulin, rTM; recombinant human thrombomodulin, rhTM; Japanese Association for Acute Medicine, JAAM.

Table 2. Baseline Data of Enrolled Patients.

Study	Country	Study design	Anticoa-gulant type	Number of patients		Age (years)		APACHEII score		SOFA score		DIC score
				Anticoagulant	Control group	Anticoagulant	Control group	Anticoagulant	Control group	Anticoagulant	Control group	
J.-F. DHAINAUT *et al*, 2004	America	Retrospective	Drotrec-ogin alfa	233	221	60.2±17.6	60.2 ±17.6	26.7±7.8	26.5±8.2	NR	NR	ISTH-DIC
J.KIENAST *et al*, 2006	Germany	Prospective	AT	20	22	55.9±18.5	53.6 ±16.1	NR	NR	NR	NR	ISTH-DIC
Satoshi Gando *et al*, 2013	Japan	Prospective	AT	30	30	67.0±17.0	73.0 ±15.0	21.4±9.2	20.4±7.1	8.5±3.4	7.8±3.4	ISTH-DIC, JAAM-DIC
Masafumi Yamato *et al*, 2013	Japan	Retrospective	rTM	14	8	72.0±2.3	70.0±2.8	NR	NR	12.0±0.8	12.0±1.9	JAAM-DIC
Jean-Louis Vincent *et al*, 2013	Belgium	Retrospective	ART-123	370	371	57.5±19.1	56.9 ±17.9	NR	NR	NR	NR	ISTH-DIC
T.TAGAMI *et al*, 2014	Japan	Retrospective	AT	2663	6412	73.8±19.4	75.9 ±19.2	NR	NR	NR	NR	JAAM-DIC
T. TAGAMI *et al*, 2015	Japan	Retrospective	rhTM	1280	5062	73.2±14.4	74.9 ±14.0	NR	NR	NR	NR	ISTH-DIC, JAAM-DIC
Akiyoshi Hagiwara *et al*, 2016	Japan	Prospective	rhTM	47	45	74.7±2.1	77.2±1.8	17.8±0.8	19.7±0.9	NR	NR	JAAM-DIC
Takeshi Wada *et al*, 2022	Japan	Retrospective	AT and/or rhTM	331	809	72.0±4.3	73.0±4.5	27.0±3.3	21.0±3.0	10.0±1.5	8.0±1.5	ISTH-DIC, JAAM-DIC

Note: Not Reported, NR; disseminated intravascular coagulation, DIC; antithrombin, AT; recombinant thrombomodulin, ART-123; recombinant thrombomodulin,rTM; recombinant human thrombomodulin, rhTM; Japanese Association for Acute Medicine, JAAM; International Society on Thrombosis and Haemostasis, ISTH; Acute Physiology and Chronic Health Evaluation, APACHEII; Sequential Organ Failure Assessment, SOFA.

Table 3. Risk of Bias in Each Study Assessed Using the MINORS Tool.

Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Total score
J.-F. DHAINAUT *et al*, 2004	2	1	2	1	2	2	2	0	2	2	2	1	19
J.KIENAST *et al*, 2006	2	2	1	1	2	2	2	0	1	1	2	1	17
Satoshi Gando *et al*, 2013	2	2	2	2	2	2	2	0	2	2	1	2	20
Masafumi Yamato *et al*, 2013	2	2	1	2	2	2	2	0	2	2	2	2	21
Jean-Louis Vincent *et al*, 2013	2	2	1	1	2	2	2	0	1	1	2	2	18
T.TAGAMI *et al*, 2014	2	2	1	1	2	2	2	0	2	2	2	1	19
T. TAGAMI *et al*, 2015	2	2	1	2	1	2	2	0	2	2	1	2	18
Akiyoshi Hagiwara *et al*, 2016	2	2	2	2	1	2	2	0	2	2	2	1	20
Takeshi Wada *et al*, 2022	2	2	2	2	2	2	2	0	2	2	2	2	22

Note: Item 1, a stated aim of the study; Item 2, inclusion of consecutive patients; Item 3, prospective collection of data; Item 4, endpoint appropriate to the study aim; Item 5, unbiased evaluation of endpoints; Item 6, follow-up period appropriate to the major endpoint; Item 7, loss to follow-up not exceeding 5%; Item 8, prospective calculation of the sample size; Item 9, a control group having the gold standard intervention; Item 10, contemporary groups; Item 11, baseline equivalence of groups; Item 12, statistical analyses adapted to the study design.

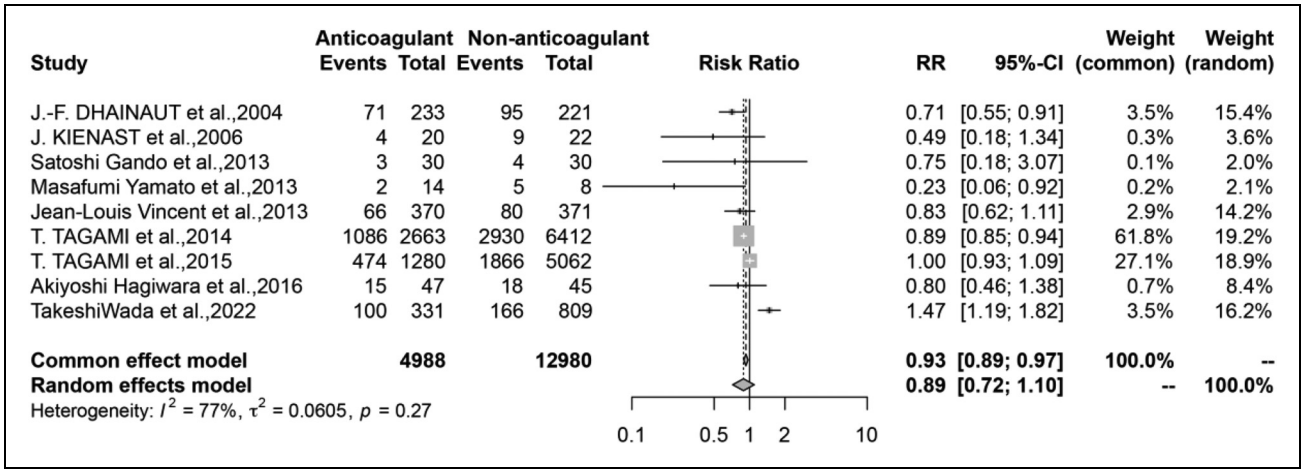

Figure 2. Forest plot of the comparison: anticoagulant versus non-anticoagulant: all-cause mortality. RR, Risk Ratio; M-H, Mantel–Haenszel; CI, confidence interval.

total scores indicated high quality. And other three studies were graded as medium quality.

Study Results

Mortality

All nine studies enrolling 17,968 patients reported mortality as a primary outcome (shown in Figure 2). Eight trials found a protective effect of anticoagulant therapy against death, only one study found null effects. We selected a random effects model because the complication rate was heterogeneous (I^2 = 77%, P = 0.27). The differences between the two groups were not statistically significant (RR: 0.89, 95% CI, 0.72–1.10).

Based on the type of anticoagulants, we conducted a subgroup analysis (shown in Figure 3). We selected a random effects model because the complication rate was heterogeneous (I^2 = 86.30%, P = 0.30). There was no statistically significant reduction in mortality (RR: 0.92, 95% CI, 0.80–1.07).

Bleeding Complications

Four studies enrolling 1297 patients reported rates of bleeding complications (shown in Figure 4). We adopted a fixed-effects model based on the P value and I^2 value. There was no significant difference between groups in the risk of bleeding complications (RR: 1.27, 95% CI, 0.77–2.09).

DIC Resolution

Three studies reported specific changes in DIC resolution rate of patients. Subgroup analysis was performed due to

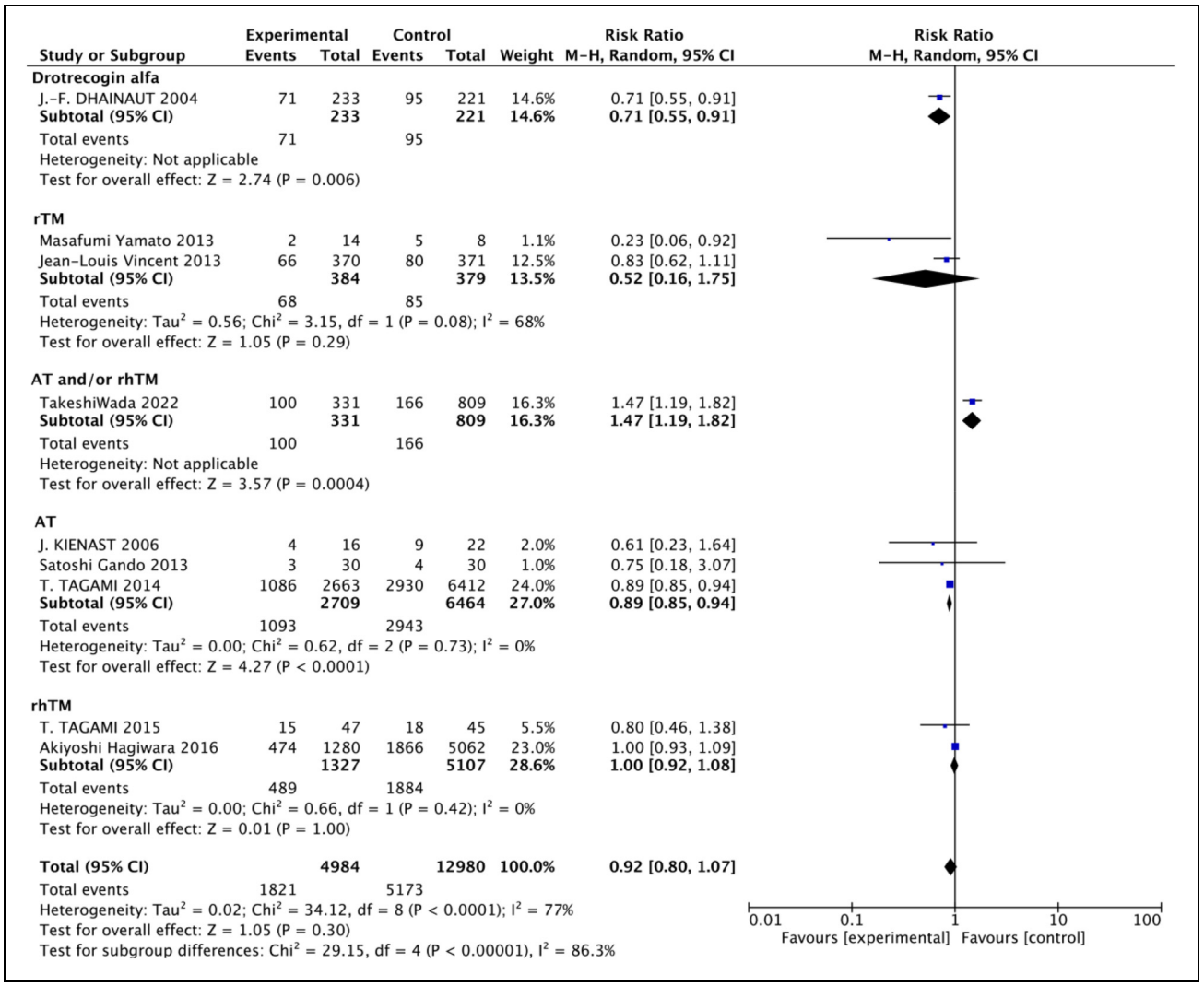

Figure 3. Forest plot of the comparison of anticoagulant therapy versus control for all-cause mortality in all eligible study patients. AT, antithrombin; rTM, recombinant thrombomodulin; rhTM, recombinant human thrombomodulin; M-H, Mantel–Haenszel; CI, confidence interval.

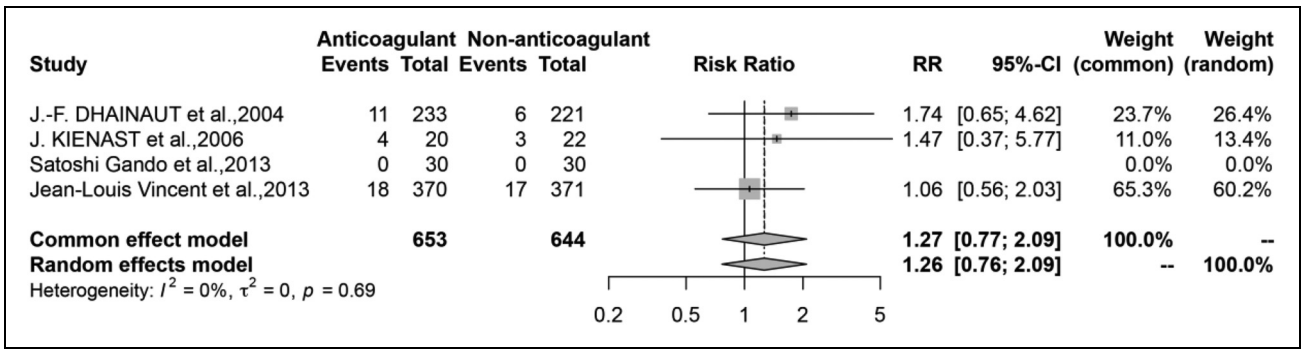

Figure 4. Forest plot of the comparison: anticoagulant versus non-anticoagulant: bleeding complications. RR, Risk Ratio; M-H, Mantel–Haenszel; CI, confidence interval.

the difference in observation time. Figure 5A shows that no matter on the day 3 or day 7 of anticoagulation therapy, the DIC resolution rate in the anticoagulation group has a statistically significant increase compared with the control group [OR: 2.62, 95% CI (1.54–4.45), $P < 0.05$, $I^2 = 10\%$].

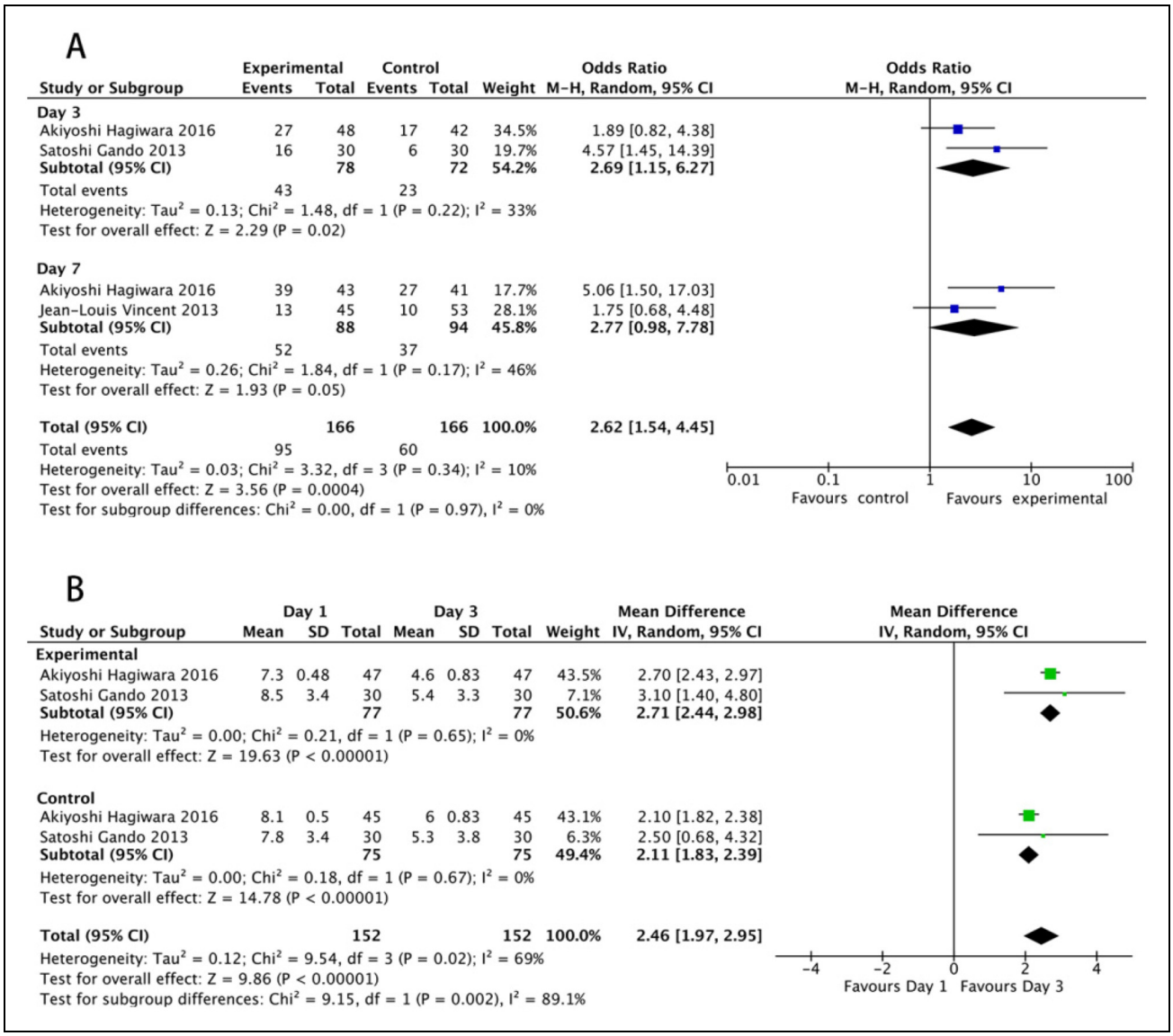

Figure 5. A, forest plot of the comparison of anticoagulant therapy versus control(non-anticoagulant) for DIC resolution rate; B, forest plot of the comparison: anticoagulant versus non-anticoagulant: SOFA score. M-H, Mantel–Haenszel; CI, confidence interval.

SOFA Score

Two of the included studies, reported the change of SOFA score. As shown in Figure 5B, the pooled analysis of relevant studies showed that SOFA scores of both control and experimental groups decreased over time [Mean = 2.46, 95% CI (1.97–2.95), $P = 0.02$, $I^2 = 69\%$]. However, there was no significant difference in score reduction between the two groups ($P = 0.13$).

Sensitivity Analysis and Publication Bias

We analyzed the sensitivity of the pooling effect of nine articles. The results were robust that there was no significant change in the pooled effect. Publication bias was evaluated using funnel plot and Egger's test. We assessed the publication bias of the main results of mortality (shown in Figure 6). A relatively symmetric funnel plot indicated no significant publication bias. The power of the Egger's test might be limited if less than 10 studies included, so that the difference between contingency and asymmetry would not be distinguished. No potential publication bias was observed in the all included studies.

Discussion

Sepsis is a systemic inflammatory response syndrome caused by various causes.[21] In recent years, despite the progress of antibiotic therapy and organ function support technology, the mortality of sepsis is still around 30%–70%.[22] The high consumption of medical resources seriously affect the quality of human life.[4] The continuous and excessive activation of inflammation could result in the uncontrolled activation of thrombosis, which represent a physiological stage in the development of DIC. Therefore,

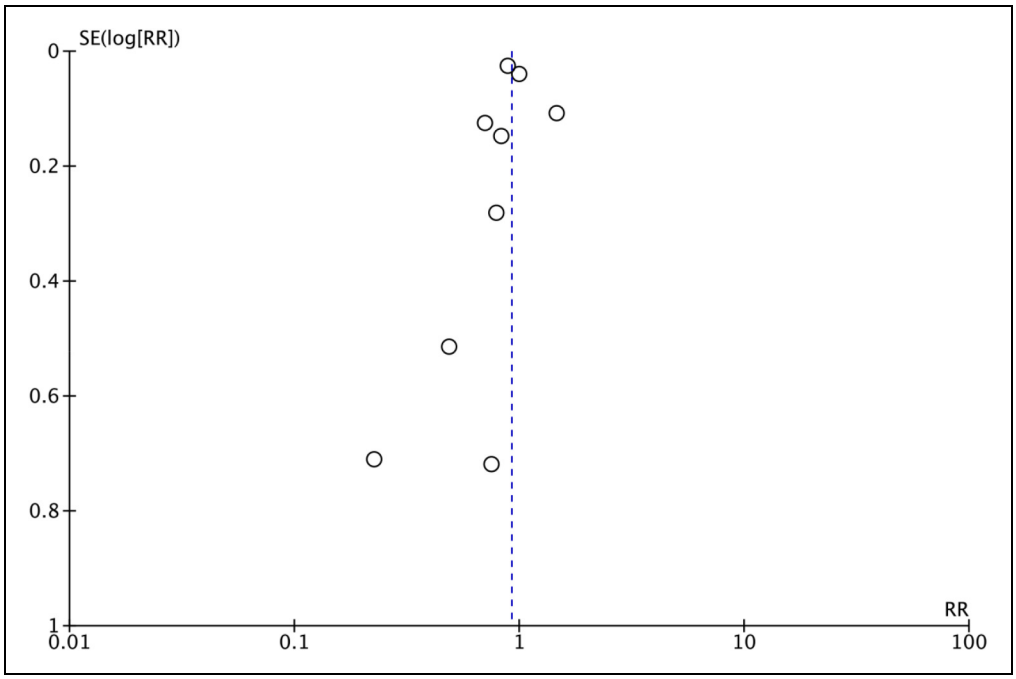

Figure 6. The publication bias of the main results of mortality. SE, standard error; RR, Risk Ratio.

anticoagulant therapy may be meaningful only for the patients with sepsis-induced DIC. JAAM-DIC score and ISTH-DIC score can be used for sepsis-induced DIC.[23]

Recently, previous study has found that endothelial activation and injury are the key driving factors of sepsis related coagulopathy. Endothelium plays an important role in balanced hemostasis.[24] The destruction of endothelial glycocalyx in sepsis lead to increased leukocyte adhesion, intravascular coagulation, tissue edema, and vascular relaxation disorder.[25] When antithrombin is combined with heparin sulfate on endothelial cells, the anticoagulant activity of antithrombin is significantly increased. A unique feature of antithrombin is that it can reduce the damage of glycocalyx. Its mechanism is speculated to be involved in binding with heparin on endothelial cells. This phenomenon can explain why the beneficial effect of antithrombin is offset by the combined use of heparin. Therefore, heparin as anticoagulant has no obvious effect on sepsis-induced DIC.[2,26]

Thrombomodulin (TM) combined with thrombin can reduce the clotting activity of thrombin and enhance the activity of activated protein C, which has anticoagulant effect. Therefore, TM is an important intravascular coagulation inhibitor that turns thrombin from procoagulant to anticoagulant. In this study, we found the potential benefits of adding recombinant thrombomodulin to antithrombin. The co-administration of these two anticoagulants was associated with a reduction mortality in sepsis-induced DIC, without an increased risk of bleeding.[27] After being activated by thrombin, recombinant human activated protein C selectively inactivates activated coagulation factors Va and V?a. After removing sodium citrate, it can inhibit thrombin production and platelet aggregation, thus preventing thrombosis.

Currently, there is no evidence that anticoagulation is effective in patients with sepsis-induced DIC.[28] In previous studies, most of the studies used anticoagulants to treat patients with sepsis or sepsis with coagulation disorder. Therefore, our study focuses not only on the general population with sepsis, but also on the specific population: the population with sepsis-induced DIC. This meta-analysis demonstrated that anticoagulant therapy had no significant benefit on mortality in populations with sepsis-induced DIC. As a secondary outcome, the risk of bleeding complications was not significantly increased in the anticoagulation group. At the same time, anticoagulation therapy can promote the DIC resolution in sepsis-induced DIC. However, patients with sepsis-induced DIC are not only at risk of blood coagulation disorder and thrombosis, but also have other organ dysfunction. Therefore, we consider that there are still other related risk factors affecting mortality.

This systematic review and meta-analysis have several limitations. First, we assume that the anticoagulants in this study are same, even though these agents have a unique anticoagulant effect and pharmacological features. Second, we do not evaluate other effects of anticoagulant, which may contribute to the outcomes. Third, there is no standardized definition of sepsis-induced DIC. Therefore, further multicenter, large-sample RCTs are needed to confirm these findings.

Conclusion

Our study observed no significant benefit of anticoagulant therapy on mortality of sepsis-induced DIC. Anticoagulation therapy can promote the resolution of DIC in sepsis-induced DIC. In addition, anticoagulant therapy does not increase the risk of bleeding in these patients. Further large rigorous RCTs are needed to confirm or refute these findings.

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Author Contributions Statement

Wenqian Qi designed and wrote the manuscript. Jingyuan LIU participated in searching and summarizing the relevant literature. Ang LI provided the theme and design, and edited the manuscript. All authors have read and approved the final manuscript.

Declaration of Conflicting Interests

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