Hypothermic Circulatory Arrest Time affects neurological outcomes of Frozen Elephant Trunk for Acute Type A Aortic Dissection: a systematic review and meta-analysis

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Abstract

Background: The treatment of complex thoracic aorta pathologies remains a challenge for cardiovascular surgeons. After introducing Frozen Elephant Trunk (FET), a significant evolution of surgical techniques has been achieved. The present meta-analysis aimed to assess the efficacy of FET in acute type A aortic dissection (ATAAD) and the effect of circulatory arrest time on post-operative neurologic outcomes. Methods: A standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses search was conducted for all observational studies of patients diagnosed with ATAAD undergoing total arch replacement with FET reporting in-hospital mortality, bleeding, and neurological outcomes. A random-effect meta-analysis was performed using STATA software (StataCorp, TX, USA). Results: Thirty-five studies were eligible for the present meta-analysis, including 3211 patients with ATAAD who underwent total arch replacement with FET. The pooled estimate for in-hospital mortality, postoperative stroke, and spinal cord injury were 7% (95% CI 5 – 9; I2 = 68.65%), 5% (95% CI 4 – 7; I2 = 63.93%), and 3% (95% CI 2 – 4; I2 = 19.56%), respectively. Univariate meta-regression revealed that with increasing the duration of hypothermic circulatory arrest time, the effect sizes for postoperative stroke and SCI enhances. Conclusions: It seems that employing the FET procedure for acute type A dissection is associated with acceptable neurologic outcomes and a similar mortality rate comparing with other aorta pathologies. Besides, increasing hypothermic circulation arrest time appears to be a significant predictor of adverse neurologic outcomes after FET.

Introduction

Utilizing "elephant trunk" (ET) prosthesis first described by Borst et al. in 1986 for aneurysmal aortic disease revolutionized treatment strategies in managing patients with complex arch and descending aorta pathologies (1). Antegrade open stent-grafting of the descending aorta described in 1996 became the cornerstone of further advancement in the arch and proximal descending aorta (2). In the early 2000s, a custom-made hybrid prosthesis called frozen elephant trunk (FET) had been developed (3). Subsequently, the FET technique has been extensively engaged in various acute and chronic pathologies of the thoracic aorta.

Replacement of the ascending aorta is a well-researched conventional treatment of acute Type A aortic dissection (ATAAD); however, residual pathology or dissection in the arch or downstream descending aorta may require additional treatment with high-risk redo procedures. On the other hand, more extensive aorta replacement (e.g., employing FET) carries the risk of complications. Therefore, there is still an ongoing debate over the optimal indication and FET use in ATAAD. One of the main complications associated with FET is neurologic events, particularly spinal cord injury (SCI) and stroke. The incidence rate of permanent or transient ischemic SCI after conventional ET has been reported between 0.4% and 2.8% in previous reports (4).

In contrast, the incidence of SCI after FET ranged between 8% in multicenter studies (5) and 20% in single-center reports (6). Several contributors (i.e., length of the device and distal circulatory arrest time) have been proposed to explain SCI and stroke observed after FET procedure, mainly derived from observational studies on patients with diverse aortic pathologies. Previous meta-analyses performed on primary studies included a mixture of cohorts diagnosed with acute or chronic dissection which differ in various aspect of treatment options and also comorbid diseases (7). Herein, we evaluated the pre-and intra-operative characteristics of patients with ATAAD undergoing the FET procedure and their associations with postoperative outcomes.

Methods

Literature Search and design

The review team developed the literature search strategy. Studies related to the subject were identified by searching electronic databases and bibliographic reference lists of relevant articles. An electronic search in PubMed/Medline, EMBASE, Scopus, and Web of Science databases was conducted from their beginning to June 2020 to identify studies reporting the outcomes of FET procedure in cohorts of patients diagnosed with ATAAD. A combination of controlled vocabulary and free text terms (utilizing Boolean operators) was used to interrogate the databases. The search was limited to English-language articles and human studies. The search strategy is presented in supplementary table 1. The present study is conducted and reported following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (8).

Eligibility Criteria of Studies and Data Extraction

Studies ascertained eligibility if those provided total aortic arch replacement with FET through median sternotomy in the ATAAD patients. Proximal arch or hemiarch procedures (i.e., procedures that did not replace the entire arch) and other pathologies (i.e., aneurysm) were excluded. Additional inclusion criteria included all observational studies reporting more than 20 patients undergoing the FET procedure and providing data for postoperative outcomes. Studies reported a combination of patients with varying pathologies was excluded if pre- and post-operative data were not reported for ATAAD individually. To exclude duplicated or overlapped populations from the same institution, these publications were identified. The latest report or those with the largest sample size without overlapped time were included in the final analysis.

After excluding case reports, conference presentations, editorials, expert opinions, and duplicated evidence, all titles and abstracts were reviewed by two independent reviewers (MM and YR), and irrelevant ones were excluded. The full-text articles were retrieved in those that met our inclusion criteria (Figure 1). The data extraction was independently performed by two authors (MM and YR). If necessary, discrepancies were resolved by consensus or discussion with the senior and corresponding authors (MB and SH). The extracted data included baseline characteristics (i.e., age, sex, cardiovascular risk factors, smoking history, prior surgery, chronic kidney disease, and history of stroke). Procedure-related features (i.e., concomitant procedures, procedure duration, cardiopulmonary bypass time, circulatory arrest time, cannulation site, and stent type) and postoperative follow-up outcomes (i.e. mortality, acute kidney injury, post-operative bleeding, transient or permanent stroke, and spinal cord injury) were also extracted and recorded.

Statistical analysis

Study features and patients' characteristics were reported. Data are presented as number (percentage) or mean and 95% confidence interval (CI), as appropriate. The pooled estimated prevalence of each outcome was calculated utilizing a random-effect model, which is more generalized when potential heterogeneity among studies is present. All values were presented with 95% confidence intervals (CI), and the weighted prevalence of outcomes is depicted as a forest plot. We assessed the homogeneity of incidence of events across studies using Cochran Q for each of the outcomes. Also, to test for heterogeneity, Higgins I^2 was calculated.I^2 represents the percentage of total variation across studies that can be attributed to heterogeneity rather than chance. The I^2 value 0% indicates no heterogeneity, 25% low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity (9). Funnel plots were drawn for all extracted outcomes to assess publication bias. Visual inspection of asymmetry was assessed to check for publication bias, and Egger's test was also conducted to evaluate small-study effects on the pooled estimated outcome (10). Moreover, Moment base univariate meta-regression was performed to assess the effects of hypothermic circulatory arrest (HCA) time on neurologic outcomes (stroke and SCI), depicted as bubble plot. All data were analyzed using STATA software (StataCorp, TX, USA).

Results

Baseline characteristics and procedural features

After reviewing shreds of evidence, a total of 35 studies including 3211 patients were entered into the quantitative analysis (Figure 1)(11-44). The median size of reviewed reports was 72 patients (interquartile range 38 – 122). The majority of studies were performed in Chinese institutions, 19 studies including 2026 patients. The patients' median age was 52 years (interquartile range 48 – 59). The frequency of male and female genders were 2268 (74.6%) and 773 (25.4%), respectively, reporting by 34 studies. Smoking (208 patients, 43.1%) and hypertension (1827 patients, 70%) were reported by seven and 29 studies. Other baseline characteristics are summarized in Table 1 and Supplementary Table 2.

Emergent/urgent surgery was implemented in 952 patients, reported by 11 studies. The cannulation site was applied in the innominate artery and the axillary artery in 3 studies (245 patients) and 20 studies (1896 patients), respectively. Bentall and David procedures were performed in 566 of 2152 patients (22 studies) and 219 of 1550 patients (14 studies). The ascending aorta replacement was applied in 364 patients, reporting by six studies. The type of stent deployed in the descending aorta included Cronus (MicroPort Medical, Shanghai, China), E-vita (JOTEC GmbH, Hechingen, Germany), Thoraflex (Vascutek, Inchinnan, UK), and Frozenix (Japan Lifeline, Tokyo, Japan) that those were implanted in 1413, 315, 250, and 161 patients, respectively. The stent type in other patients is also provided in Table 2. Only 342 patients in four studies reported the use of near-infrared spectroscopy during surgery. The median of HCA time was 31 min (interquartile range 25 – 35), reported by 19 studies. Other surgery-related features are summarized in Table 2.

Follow-up outcomes

The pooled estimates of postoperative stroke and SCI were 5% (95% CI 4 – 7; $I^2 = 63.93\%$) and 3% (95% CI 2 – 4; $I^2 = 19.56\%$), respectively (Figure 2). The pooled estimates of acute kidney injury, bleeding, and in-hospital mortality were found to be 12% (95% CI 9 – 15;$I^2 = 86.65\%$), 6% (95% CI 3 – 8;$I^2 = 71.05\%$), and 7% (95% CI 5 – 9;$I^2 = 68.65\%$), respectively (Figure 3).

Publication bias and meta-regression

The visual inspection of Funnel plots revealed asymmetries among studies reporting major postoperative outcomes (Supplemental Figure 1). Based on the Egger's test, there were significant for all major outcomes, including postoperative stroke ($p < 0.0001$), SCI ($p = 0.004$), acute kidney injury ($p < 0.0001$), bleeding ($p < 0.0001$), and in-hospital mortality ($p < 0.0001$). The univariate meta-regression showed significant relationships between the HCA time and the development of postoperative stroke ($p = 0.04$) and SCI ($p = 0.05$). Also, the bubble plots revealed that with increasing HCA time, the effect sizes for postoperative stroke and SCI enhance. The regression line provides a good fit for the data because most studies are relatively close (Figure 4).

Discussion

Nowadays, the most common indication for FET is chronic or acute dissection that involved the ascending aorta followed by degenerative atherosclerosis aneurysm (45). The FET procedure is now potentially indicated for varying aortic arch and descending aorta pathologies, including chronic or acute dissection as well as aneurysmal pathologies. It is well established that each pathology is associated with specific risk profiles, affecting short- and long-term outcomes after aortic arch repair (46). In addition to the type of aorta pathology, cannulation site, concomitant surgery, neurological monitoring, the method surgeon approached to the left subclavian artery, and intra-operative measures would change the course of postoperative outcomes. So, we herein conducted a systematic review focused on the outcome of FET deployment in ATAAD patients who needs total arch replacement, taking into account peri-operative features.

The present meta-analysis, including 35 studies with 3211 patients diagnosed with ATAAD, revealed that the FET procedure in this subset of patients was associated with 3% (95% CI 2 – 4) and 5% (95% CI 4 – 7) of postoperative SCI and stroke, respectively. Additionally, the pooled rate of in-hospital mortality was found to be 7%. A recent meta-analysis by Preventza et al. demonstrated a total pooled operative mortality of 8.8% from 34 reports on patients undergoing FET procedure (7) comparable with rates reported by other meta-analyses (47, 48). In the present meta-analysis, we found that the pooled estimate of in-hospital mortality was 7% (95% CI 5 – 9;$I^2 = 68.65\%$) which is less than previous reports. One possible explanation is that they estimated operative mortality (variously reported operative, 30-day, and in-hospital), not specifically in-hospital mortality estimated in our analysis. Another drawback regarding previous reports is that they included heterogenous populations with different pathologies or chronicity of dissection in the final analysis. Although they tried to address this issue by subgroup analysis (7), only 12 studies on patients with ATAAD have been compared with other pathologies (14 studies). Besides, recent meta-analyses (47, 48) included a mixture of patients who underwent total arch replacement, proximal, and hemi arch replacement; meanwhile, they reported a higher mortality rate. It is noteworthy that total arch replacement is a more complex surgery. Hence, total arch replacement in an urgent or emergent situation inheres with a greater peri-operative mortality rate. The observed discrepancy and declining mortality rate during recent years may be attributed to improved diagnostic modalities, enhanced experience of aortic centers and aortic surgeons, and well-established monitoring techniques (49).

Despite the improved results of extensive aortic surgery since the introduction of HCA and brain protection techniques, these procedures are still associated with neurologic impairments. Neurologic complications such as stroke and SCI are the most disastrous complication of aortic surgery, especially after thoracic and arch procedures, with a high burden of morbidity and health-related costs (50). In a single-center series of 25 patients who underwent thoracic aorta aneurysm repair with FET, 24% of patients developed SCI after surgery which is a significant rate of this dreaded complication (6). On the other hand, data from multicenter studies revealed a considerably lower rate of stroke and SCI. A report from the International E-vita Open Registry (IEOR) indicated a 6% and 8% incidence rate of stroke and SCI, respectively (5). We found that the pooled estimate for overall stroke reported in 24 studies was 5%, and 3% for SCI reported in 16 studies. A different definition of SCI and diagnostic criteria and distinct baseline characteristics could explain the inconsistency observed amongst previous reports. However, the impact of the indication of total arch replacement (ATAAD versus chronic dissection and aneurysm) is arguable. This was the main rationale behind including only studies of patients diagnosed with ATAAD in the present meta-analysis. Several hypotheses proposed to explain SCI after FET, including the level of distal landing zone of the stent, hemodynamic instability after cardiopulmonary bypass, age, compromising segmental spinal cord blood supply, and HCA time (6, 51, 52). The effect of the distal stent landing zone on the incidence of SCI has been explored previously; however, different results indicated the possibility of other contributing factors (6, 53). We examined the effect of HCA time on the development of neurologic adverse events. Nowadays, isolated HCA as a protective strategy is not recommended (36). Recent publications indicate that milder hypothermic circulatory arrest in combinations of routine selective antegrade cerebral perfusion improves brain and end-organ protection (54). Unfortunately, we could not evaluate the relationship between core temperature during arch replacement and neurologic events due to lack of data and inconsistency between reports regarding measurements. A total of 19 studies reported circulatory arrest time, and we observed that with a longer duration of circulatory arrest time, a higher rate of neurologic adverse events would be expected. A similar concern regarding the role of HCA time has been raised by Tian et al. while they found a significant strong positive linear relationship between mortality and circulatory arrest time (r = 0.715) (48). Hence, companies and surgeons endeavor to simplify the anastomosis of the prosthesis to the distal aortic stump allowing less HCA time and starting rewarming swiftly (55). In addition to the HCA time, the degree of hypothermia and cerebral perfusion method to achieve the best neurologic outcome is of paramount (56). In the present series of studies included in the meta-analysis, only four authors did not mentioned the cerebral perfusion method, while in all other reports antegrade cerebral perfusion has been utilized.

Limitations

The present findings are limited by several key constraints which should be considered when interpreting the results. Firstly, all the studies were retrospective, and the main results are based on non-randomized observational studies, which impose a considerable selection bias. Secondly, due to the lack of a standard reporting schema for total arch replacement using FET, some important data are missing, which incapacitates us to perform subgroup analysis.

Conclusions

In summary, the FET procedure provides an optimal option with an acceptable rate of mortality and adverse neurologic events. As FET is gaining more popularity for aortic arch and proximal descending aorta procedures, the magnitude of operative adjuncts on the outcomes became more apparent. A lot of effort must be put into reducing HCA time and improving device profile to achieve the minimum time for graft anastomosis.

Conflict of interests

The authors have none to declare.

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Figure legends

Figure 1- PRISMA flow diagram

Figure 2- Pooled estimates of (A) postoperative stroke and (B) SCI

Figure 3- Pooled estimates of (A) acute kidney injury, (B) bleeding, and (C) in-hospital mortality

Figure 4- The graph shows the effect sizes for (A) postoperative stroke and (B) SCI plotted against the HCA time. The regression line and corresponding confidence intervals are plotted

Supplementary Figure 1- Funnel plots showing the publication bias for (A) postoperative stroke, (B) SCI, (C) acute kidney injury, (D) bleeding, and (E) in-hospital mortality

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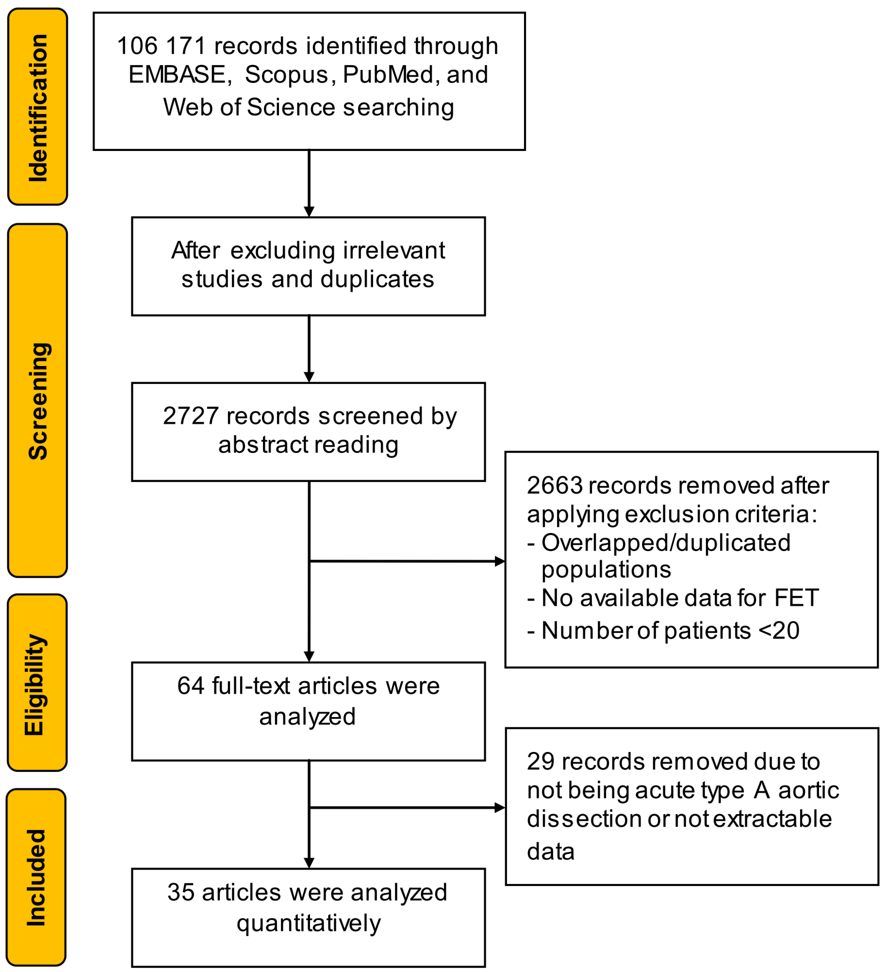
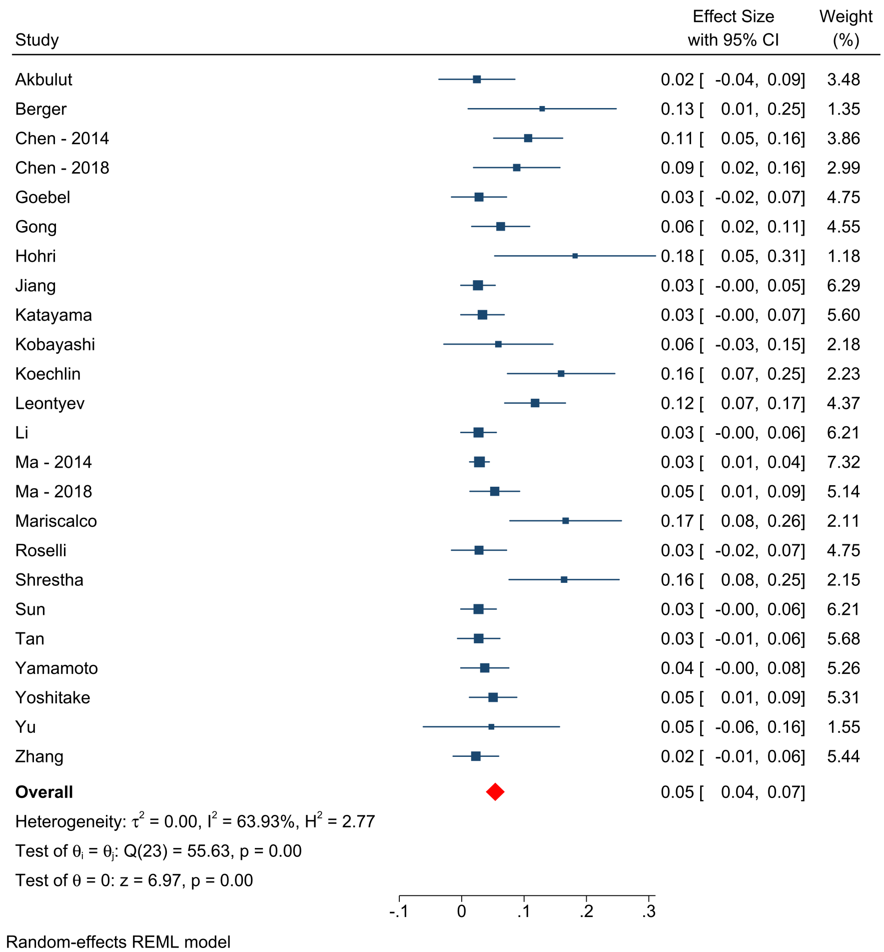
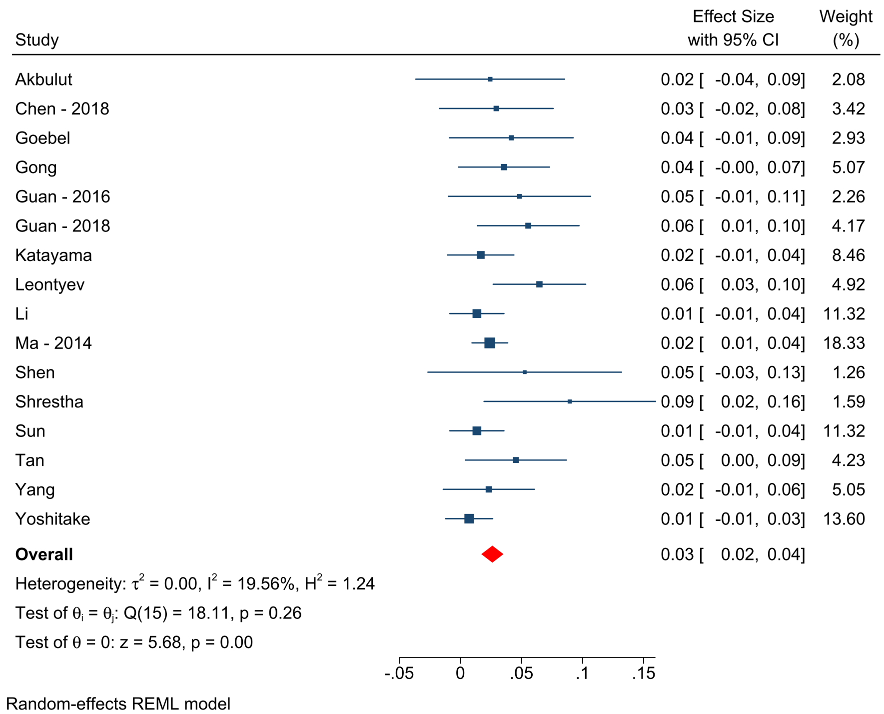
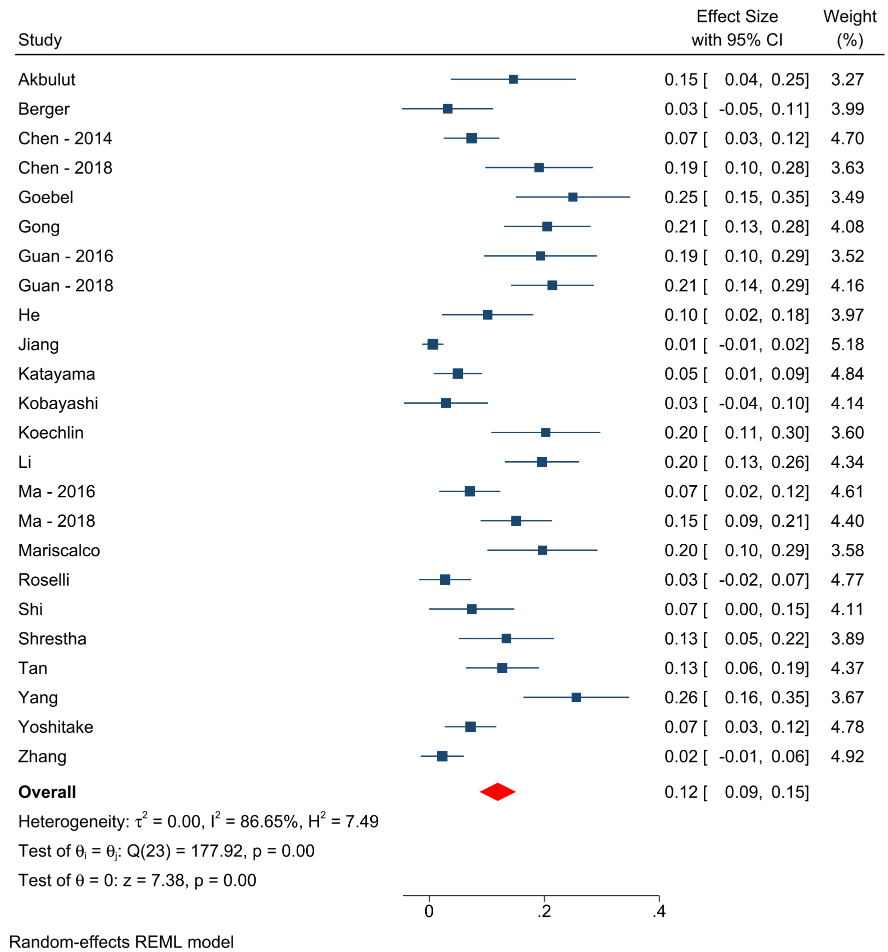
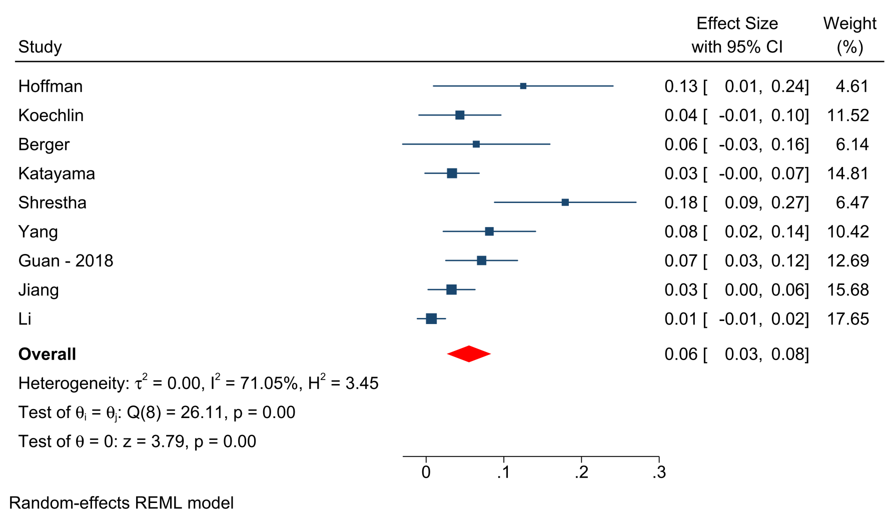
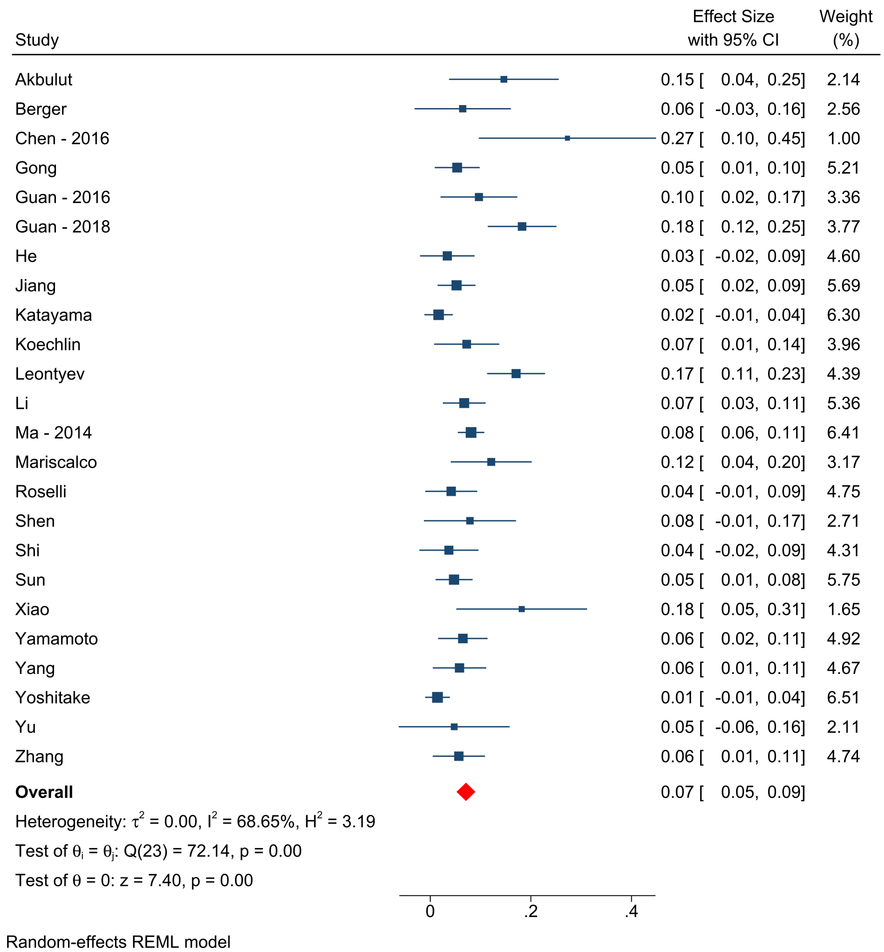


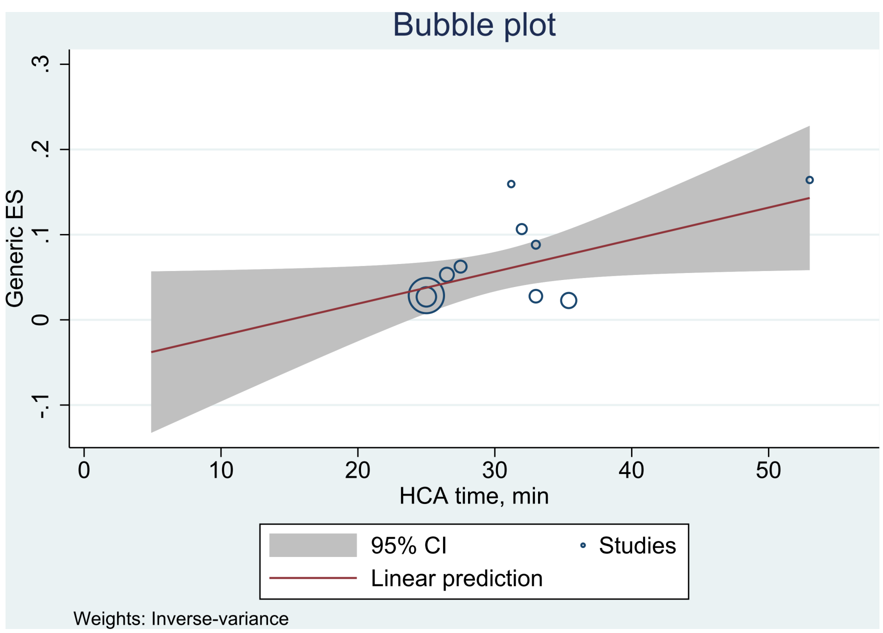

Study
Effect Size with 95% CI
Weight (%)
Akbulut 0.02 [-0.04, 0.09] 3.48
Berger 0.13 [0.01, 0.25] 1.35
Chen - 2014 0.11 [0.05, 0.16] 3.86
Chen - 2018 0.09 [0.02, 0.16] 2.99
Goebel 0.03 [-0.02, 0.07] 4.75
Gong 0.06 [0.02, 0.11] 4.55
Hohri 0.18 [0.05, 0.31] 1.18
Jiang 0.03 [-0.00, 0.05] 6.29
Katayama 0.03 [-0.00, 0.07] 5.60
Kobayashi 0.06 [-0.03, 0.15] 2.18
Koechlin 0.16 [0.07, 0.25] 2.23
Leontyev 0.12 [0.07, 0.17] 4.37
Li 0.03 [-0.00, 0.06] 6.21
Ma - 2014 0.03 [0.01, 0.04] 7.32
Ma - 2018 0.05 [0.01, 0.09] 5.14
Mariscalco 0.17 [0.08, 0.26] 2.11
Roselli 0.03 [-0.02, 0.07] 4.75
Shrestha 0.16 [0.08, 0.25] 2.15
Sun 0.03 [-0.00, 0.06] 6.21
Tan 0.03 [-0.01, 0.06] 5.68
Yamamoto 0.04 [-0.00, 0.08] 5.26
Yoshitake 0.05 [0.01, 0.09] 5.31
Yu 0.05 [-0.06, 0.16] 1.55
Zhang 0.02 [-0.01, 0.06] 5.44
Overall 0.05 [0.04, 0.07]
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 63.93\%$, $H^2 = 2.77$
Test of $\theta_i = \theta_j$: Q(23) = 55.63, p = 0.00
Test of $\theta = 0$: z = 6.97, p = 0.00
-.1 0 .1 .2 .3
Random-effects REML model

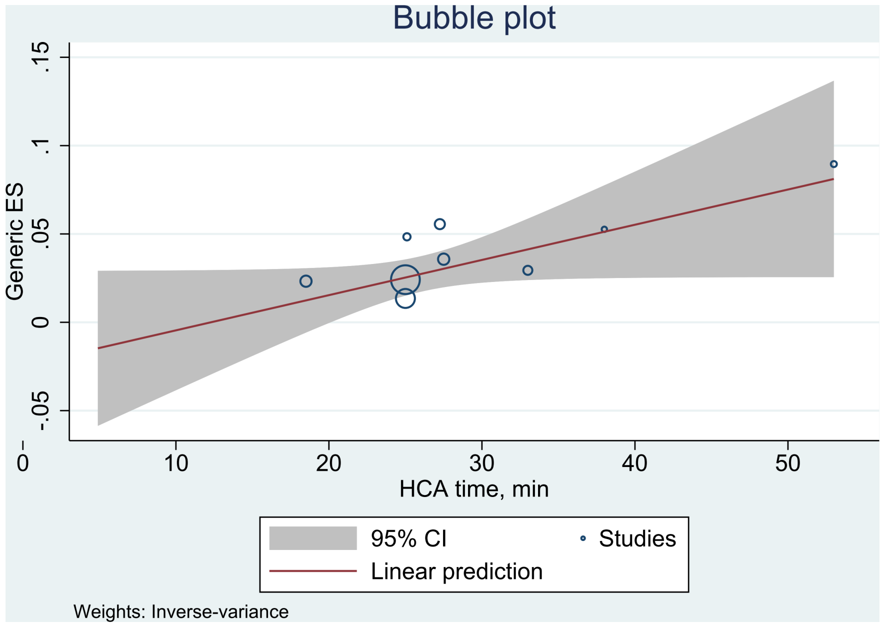

Study
Effect Size with 95% CI
Weight (%)
Akbulut 0.02 [-0.04, 0.09] 2.08
Chen - 2018 0.03 [-0.02, 0.08] 3.42
Goebel 0.04 [-0.01, 0.09] 2.93
Gong 0.04 [-0.00, 0.07] 5.07
Guan - 2016 0.05 [-0.01, 0.11] 2.26
Guan - 2018 0.06 [0.01, 0.10] 4.17
Katayama 0.02 [-0.01, 0.04] 8.46
Leontyev 0.06 [0.03, 0.10] 4.92
Li 0.01 [-0.01, 0.04] 11.32
Ma - 2014 0.02 [0.01, 0.04] 18.33
Shen 0.05 [-0.03, 0.13] 1.26
Shrestha 0.09 [0.02, 0.16] 1.59
Sun 0.01 [-0.01, 0.04] 11.32
Tan 0.05 [0.00, 0.09] 4.23
Yang 0.02 [-0.01, 0.06] 5.05
Yoshitake 0.01 [-0.01, 0.03] 13.60
Overall 0.03 [0.02, 0.04]
Heterogeneity: τ^2 = 0.00, I^2 = 19.56%, H^2 = 1.24
Test of $\theta_i = \theta_j$: Q(15) = 18.11, p = 0.26
Test of θ = 0: z = 5.68, p = 0.00
-.05
0
.05
.1
.15
Random-effects REML model


Study
Effect Size with 95% CI
Weight (%)
Akbulut 0.15 [0.04, 0.25] 3.27
Berger 0.03 [-0.05, 0.11] 3.99
Chen - 2014 0.07 [0.03, 0.12] 4.70
Chen - 2018 0.19 [0.10, 0.28] 3.63
Goebel 0.25 [0.15, 0.35] 3.49
Gong 0.21 [0.13, 0.28] 4.08
Guan - 2016 0.19 [0.10, 0.29] 3.52
Guan - 2018 0.21 [0.14, 0.29] 4.16
He 0.10 [0.02, 0.18] 3.97
Jiang 0.01 [-0.01, 0.02] 5.18
Katayama 0.05 [0.01, 0.09] 4.84
Kobayashi 0.03 [-0.04, 0.10] 4.14
Koechlin 0.20 [0.11, 0.30] 3.60
Li 0.20 [0.13, 0.26] 4.34
Ma - 2016 0.07 [0.02, 0.12] 4.61
Ma - 2018 0.15 [0.09, 0.21] 4.40
Mariscalco 0.20 [0.10, 0.29] 3.58
Roselli 0.03 [-0.02, 0.07] 4.77
Shi 0.07 [0.00, 0.15] 4.11
Shrestha 0.13 [0.05, 0.22] 3.89
Tan 0.13 [0.06, 0.19] 4.37
Yang 0.26 [0.16, 0.35] 3.67
Yoshitake 0.07 [0.03, 0.12] 4.78
Zhang 0.02 [-0.01, 0.06] 4.92
Overall 0.12 [0.09, 0.15]
Heterogeneity: τ^2 = 0.00, I^2 = 86.65%, H^2 = 7.49
Test of $\theta_i = \theta_j$: Q(23) = 177.92, p = 0.00
Test of θ = 0: z = 7.38, p = 0.00
0 .2 .4
Random-effects REML model


Study
Effect Size with 95% CI
Weight (%)
Hoffman 0.13 [0.01, 0.24] 4.61
Koechlin 0.04 [-0.01, 0.10] 11.52
Berger 0.06 [-0.03, 0.16] 6.14
Katayama 0.03 [-0.00, 0.07] 14.81
Shrestha 0.18 [0.09, 0.27] 6.47
Yang 0.08 [0.02, 0.14] 10.42
Guan - 2018 0.07 [0.03, 0.12] 12.69
Jiang 0.03 [0.00, 0.06] 15.68
Li 0.01 [-0.01, 0.02] 17.65
Overall 0.06 [0.03, 0.08]
Heterogeneity: τ^2 = 0.00, I^2 = 71.05%, H^2 = 3.45
Test of $\theta_i = \theta_j$: Q(8) = 26.11, p = 0.00
Test of θ = 0: z = 3.79, p = 0.00
0 .1 .2 .3
Random-effects REML model


Study
Effect Size with 95% CI
Weight (%)
Akbulut 0.15 [0.04, 0.25] 2.14
Berger 0.06 [-0.03, 0.16] 2.56
Chen - 2016 0.27 [0.10, 0.45] 1.00
Gong 0.05 [0.01, 0.10] 5.21
Guan - 2016 0.10 [0.02, 0.17] 3.36
Guan - 2018 0.18 [0.12, 0.25] 3.77
He 0.03 [-0.02, 0.09] 4.60
Jiang 0.05 [0.02, 0.09] 5.69
Katayama 0.02 [-0.01, 0.04] 6.30
Koechlin 0.07 [0.01, 0.14] 3.96
Leontyev 0.17 [0.11, 0.23] 4.39
Li 0.07 [0.03, 0.11] 5.36
Ma - 2014 0.08 [0.06, 0.11] 6.41
Mariscalco 0.12 [0.04, 0.20] 3.17
Roselli 0.04 [-0.01, 0.09] 4.75
Shen 0.08 [-0.01, 0.17] 2.71
Shi 0.04 [-0.02, 0.09] 4.31
Sun 0.05 [0.01, 0.08] 5.75
Xiao 0.18 [0.05, 0.31] 1.65
Yamamoto 0.06 [0.02, 0.11] 4.92
Yang 0.06 [0.01, 0.11] 4.67
Yoshitake 0.01 [-0.01, 0.04] 6.51
Yu 0.05 [-0.06, 0.16] 2.11
Zhang 0.06 [0.01, 0.11] 4.74
Overall 0.07 [0.05, 0.09]
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 68.65\%$, $H^2 = 3.19$
Test of $\theta_i = \theta_j$: Q(23) = 72.14, p = 0.00
Test of $\theta = 0$: z = 7.40, p = 0.00
0
.2
.4
Random-effects REML model


Bubble plot
Generic ES
-.1
0
.1
.2
.3
0
10
20
30
40
50
HCA time, min
95% CI
Studies
Linear prediction
Weights: Inverse-variance



Bubble plot
Generic ES
.15
.1
.05
0
-.05
0
10
20
30
40
50
HCA time, min
95% CI
Studies
Linear prediction
Weights: Inverse-variance