Correlation of Coagulopathy and Frozen Elephant Trunk Use in Aortic Arch Surgery: A Systematic Review and Meta-analysis

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Abstract

Background: The advent of Frozen elephant trunk (FET) for reconstruction of elective and non-elective aortic arch surgery has augmented the treatment of complex aortic pathologies in a single-stage operation. To date, no studies have been focused on the prevalence and predictors of coagulopathy potentiated by FET procedure. Methods: In a systematic review, we searched databases up to June 2020 for studies reporting coagulopathy complications after FET procedure. A proportional meta-analysis was carried out using STATA software (StataCorp, TX, USA). Results: In total, 46 studies including 6313 patients were eligible. The pooled estimation of reoperation for postoperative bleeding was 7% (95% confidence interval [CI] 5 to 8; I2 = 84.73%; reported by 39 studies including 4796 patients). The mean volume of transfused packed blood cells and fresh frozen plasma was 1677 ml (95% CI 1066.4-2287.6) and 1016.5 ml (95% CI 450.7-1582.3). The subgroup by stent type showed a decrease in the heterogeneity (I2 = 0.01%, I2 = 53.95%, I2 = 0.01%, and I2 = 54.41% for Thoraflex® Hybrid, E-vita®, Frozenix®, and Cronus®, respectively). The subgroup by chronicity of operation resulted in less heterogeneity among patients undergoing elective compared to non-elective operation (I2 = 29.22% versus I2 = 80.56% in non-elective). Meta-regression analysis showed that age and male gender significantly impacted on the reoperation for postoperative bleeding. Conclusions: The FET procedure for arch replacement is associated with coagulopathy and the transfusion of blood products. Male, age, and selective choice of FET use were identified as heterogeneity sources of reoperation for postoperative bleeding.

Introduction

Open elective and non-elective aortic surgery have proven track record in reducing mortality related intimal aortic disruption, however and despite timely and specialized aortic surgical interventions, mortality and morbidity remain inconsistent and wavering on multiple factors. Amongst, the use of cardiopulmonary bypass and hypothermic circulatory arrest are associated with coagulation related adverse events.[1] Moreover, coagulopathy is related to urgency or setting of the operation. Nonetheless, studies also correlated coagulopathy to type of pathology, urgency, predictors implicating bleeding intraoperatively and post-operatively. However, no robust evidence exists to implicate utilization of aortic arch device technologies in the causation of coagulopathy and the correlation to performance, applicability, and type of frozen elephant trunk use. To this end, and given the rapid surge of device technologies application and use in aortic arch surgery, we sought to explore the development of coagulopathy and correlate this to type of FET highlighting potential predictors to help aid clinical decision making and framework.

Methods

Database searching strategy

Electronic database searches were performed with EMBASE, Scopus, and PubMed/Medline from inception to June 2020. In addition to these databases, the bibliographies of relevant reports and Google Scholar were also used to find studies. The searching keywords were applied using a Boolean strategy (Supplementary Table 1). The searching citations were limited to human-based reports and the English language. In addition, the bibliographies of relevant studies and review articles were manually searched.

Selection Criteria

Studies providing outcomes of the FET procedure were included in the meta-analysis. The FET procedure used for total arch replacement (TAR) among various aortic pathologies (acute dissection, chronic dissection, and aneurysm) in which the open sternotomy was carried out. Inclusion criteria included studies reporting more than 20 patients undergoing the FET procedure and providing data for postoperative outcomes. Studies were excluded if they included a case report, or small case series, reviews, or editorials. Institutions that published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete reports were included for quantitative assessment at each time interval. Publications from overlapped or duplicated populations were also excluded. Studies from the same center were used in the review if the report had the highest sample size with no overlapped participants. IRB approval was not required as our study did not involve human contact or require patient consent, as the data analysed are available online via public repositories.

Data Extraction and Critical Appraisal

All titles and abstracts were reviewed by two independent reviewers. All full-texts met inclusion criteria were reviewed, and required data were also extracted. The extraction of data was performed by two independent reviewers, and if necessary, a third one was consulted. Data consisted of baseline characteristics, procedural features, and patients' outcomes during follow-up period. The extracted factors related to the coagulopathy included the number of patients with postoperative bleeding, the number of patients undergoing reoperation for postoperative bleeding, and the amount of blood products transfusion (i.e., packed blood cells and fresh frozen plasma). The volume of transfused blood products was calculated as milliliter reported by studies, and each of packed cells was considered as 250 ml. The length of stent deployed in the descending aorta was categorized into two groups (less than or equals to 10 cm or more than 10 cm).

The mean length of stent reported by studies was applied for categorization. The type of surgery was also defined as elective or non-elective (i.e., emergency/urgent) so that studies with all patients undergoing elective or non-elective operations were identified, and those with a mixture of elective and non-elective operations did not enter into this categorization. In addition, we divided patients into groups by the stent type (i.e., Thoraflex Hybrid, E-vita, Frozenix, and Cronus) and the gender predominance among studies (we categorized into two groups based on the median of male percentage, [?]74% versus >74%). In all steps of systematic review, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were used.[2]

Statistical analysis

All analyses were performed using the STATA software (StataCorp, TX, USA). All extracted data are summarized as mean (±SD) and number (percentage). All values were concomitantly presented with 95% confidence interval (CI). Median values for continuous variables were converted into mean values.[3] The weighted prevalence of endpoints during follow-up was calculated using the random-effects model and was presented as forest plots. To estimate the percentage of variation across studies, the Cochrane Q test was calculated and reported as the I^2 statistic. The I^2 value was classified into low heterogeneity (I^2 = 25% to 49%), moderate heterogeneity (I^2 = 50% to 74%), or high heterogeneity (I^2>75%).[4] To address heterogeneities, subgroup analyses using the Z-test were conducted. The test compared groups for estimation of the subgroup effect sizes and subgroup effects on heterogeneity. A meta-regression analysis was also conducted to find the potential effects of variables (i.e., age, gender, hypothermic circulatory arrest time, and the chronicity of surgery) on the pooled outcome. Publication bias was also estimated via the funnel plot visual inspection and the Begg's test.

Results

Study selection and characteristics

After application of inclusion and exclusion criteria, a total of 46 studies[5-50] consisting of 6313 patients included in this meta-analysis (Figure 1). The patients' mean age was 57.5 (95% CI 55.1 to 55.9). The frequency of males and females was 73% (95% CI 70 to 76) and 27% (95% CI 23.8 to 30), respectively, reporting by forty-five studies. The cumulative frequency of acute dissection, chronic dissection, and aneurysm in studies reporting aortic pathologies was 72.5% (95% CI 60.1 to 84.2), 36.2% (95% CI 24 to 48.4), and 48.2% (95% CI 34.1 to 62.3), respectively. The prevalence of prior cerebrovascular accidents and chronic kidney disease was 7.7% (95% CI 5.3 to 10.1) and 12.5 % (95% CI 5.4 to 19.7), respectively. The FET hybrid stent graft is mostly used in China (17 studies including 3314 patients), Japan (8 studies including 526 patients), and Germany (8 studies including 425 patients). Other baseline characteristics are summarized in Table 1 and Supplementary Table 2.

A total of 258 and 1000 patients underwent only elective or only emergent/urgent surgeries in 7 and 10 studies, respectively. Concomitant Bentall and David surgeries were performed in 22.2% (95% CI 15.6 to 28.8) and 10.7% (95% CI 5.6 to 15.7) of patients reporting by 27 and 21 studies, respectively. The mostly used FET stents included Cronus® (MicroPort Medical, Shanghai, China), E-vita® (JOTEC GmbH, Hechingen, Germany), and Thoraflex Hybrid(r) (Vascutek, Inchinnan, UK) in 3194, 1612, 1011 patients, respectively. Other surgical features were summarized in Table 2.

Pooled estimates of outcomes

The means of hospital and intensive care unit length of stay were 16.9 (95% CI 13 to 20.8; reported by eighteen studies including 2806 patients) and 5.1 (95% CI 4 to 6.2; reported by twenty-two studies including 2975 patients) days, respectively. The pooled estimation of reoperation for postoperative bleeding was 7% (95% CI 5 to 8; $I^2 = 84.73\%$; reported by thirty-nine studies including 4796 patients; Figure 2). The number of patients with postoperative bleeding was reported by five studies including 469 patients, and pooled estimation was 17% (95% CI 7 to 28; $I^2 = 87.6\%$; Figure 3). The mean volume of transfused packed blood cells and fresh frozen plasma was 1677 ml (95% CI 1066.4 to 2287.6; reporting by fifteen studies including 2375 patients) and 1016.5 ml (95% CI 450.7 to 1582.3; reporting by ten studies including 2097 patients). The rate of in-hospital mortality was 8% (95% CI 6 to 10; $I^2 = 79.34\%$) based on the pooled proportion from thirty studies including 4272 patients (Supplementary Figure 1).

Subgroup analyses

Subgroup analyses were performed using the stent length ([?]10 cm versus >10 cm), the stent type (Thoraflex(r)Hybrid, E-vita(r), Frozenix(r), and Cronus(r)), male predominance ([?]74% versus >74% male), and the chronicity of the operation (elective versus non-elective). The categorization by the stent length led to pooled estimates associated with a lower heterogeneity regarding reoperation for bleeding among those implanted longer device (6% [95% CI 2 to 10]; $I^2 = 79.36\%$ in [?]10 cm versus 8% [95% CI 5 to 11]; $I^2 = 65.74\%$ in >10 cm); however, the test of group differences for reoperation for bleeding was non-significant (p=0.45; Figure 4). The subgroup by the stent type showed substantial decrease in the heterogeneity ($I^2 = 0.01\%$ for Thoraflex Hybrid, $I^2 = 53.95\%$ for Evita, $I^2 = 0.01\%$ for Frozenix, and $I^2 = 54.41\%$ for Cronus; Figure 5) and a significant difference between groups (p = 0.001). However, no effect on heterogeneity was observed in subgroups by the male predominance (Figure 6). The subgroup by the chronicity of operation also resulted in less heterogeneity among patients undergoing elective compared to non-elective operations (8% [95% CI 3 to 13]; $I^2 = 29.22\%$ in elective versus 6% [95% CI 3 to 9]; $I^2 = 80.56\%$ in non-elective; Figure 7). The effect of subgroup analyses on the pooled rate of in-hospital mortality was more pronounced. The heterogeneities improved among patients implanted stent >10 cm compared to those implanted stent [?]10 cm ($I^2 = 0.06\%$ versus $I^2 = 81.90\%$; Supplementary Figure 2-A). The categorization by the stent type led to substantial improvement of heterogeneity ($I^2 = 0\%$ for Thoraflex Hybrid, $I^2 = 0.06\%$ for Frozenix, $I^2 = 0.01\%$ for Evita and $I^2 = 42.48\%$ for Cronus(r), Supplementary Figure 2-B). However, the subgroups by the male predominance did not significantly decrease the heterogeneity (Supplementary Figure 2-C). Moreover, it disappeared among patients undergoing elective surgeries compared to those undergoing non-elective surgeries ($I^2 = 0\%$ versus $I^2 = 66.18\%$; Supplementary Figure 2-D). When excluding two of five studies with a wide 95% CI for the number of patients with postoperative bleeding,[31,44]the heterogeneity was significantly improved 11% (95% CI 8 to 15; $I^2 = 12.97\%$).

Meta-regression

In univariable meta-regression analysis, there was no significant association between the hypothermic circulatory arrest time and the reoperation for bleeding (β-coefficient 0.007 [95% CI -0.004 to 0.0019], z-value = 1.26, p = 0.207). In addition, the bubble plot demonstrated that the effect size of reoperation for postoperative bleeding enhanced with increasing the duration of hypothermic circulatory arrest time; however, the regression line did not show a good fit of the data because most studies were relatively far to it (Figure 8).

Multivariable meta-regression analysis showed that age and male gender significantly impacted on the reoperation for postoperative bleeding (Table 3).

Publication bias

Based on the visual inspection of the funnel plots and the Begg's test, there was asymmetry among studies reporting reoperation for bleeding and the test was significant (p = 0.0012; Supplementary Figure 3-A). There was no publication bias among studies reporting the number of patients with postoperative bleeding (p = 0.4624; Supplementary Figure 3-B). Moreover, publication bias was detected among studies reporting in-hospital mortality (p = 0.0153; Supplementary Figure 3-C).

Discussion

The FET procedure is a promising and an evolving technique that is associated with acceptable rates of mortality and morbidity compared to the conventional elephant trunk procedure in the management of complex thoracic aortic pathologies.[51] The development of coagulopathy (i.e., reoperation for bleeding and blood products transfusion) in aortic surgery is commonly observed in patients undergoing repair of aneurysm or dissection.[52,53]According to a position paper reported by the Vascular Domain of EACTS, postoperative re-exploration because of bleeding ranged between 2.5-30%.[54] The association between CPB or HCA duration and perioperative coagulopathy risk is well-documented and reported in literature. Mazzeffi et al. highlight that DHCA duration and the need for RBC transfusion are closely associated, and that this is even more pronounced with CPB durations between 120 and 180 minutes.[55] Similarly, decreased platelet count and function are well-documented sequelae of pediatric cardiac and aortic reconstruction involving CPB and DHCA.[56, 57]

No studies have explored the prevalence of coagulopathy specifically in patients undergoing arch replacement using the FET technique. In their meta-analysis, Tian et al. documented the safety and efficacy of the frozen elephant trunk technique and reported a pooled mortality of 8.3%, stroke rate of 4.9%, and spinal cord injury rate of 5.1%.[58] Though the findings of Tian et al. are robust, our study demonstrated a strong association between the FET procedure for total arch replacement and perioperative coagulopathy, represented by reoperation for postoperative bleeding and the need for blood product transfusion. 17% of the patients included suffered postoperative bleeding, while the pooled estimate of reoperation for postoperative bleeding was 7%.

The mean volumes of transfused packed blood cells and fresh frozen plasma were 1677 ml and 1016 ml respectively.

The pathophysiology of surgery-induced coagulopathy in aortic operations has not been properly described; however, it has been reported that acute aortic dissection itself activates hemostatic systems before surgery.[23] Liu et al[59] evaluated perioperative consumption coagulopathy among sixty-six patients with acute type A aortic dissection against thirty-six patients with thoracic aortic aneurysms. They demonstrated that clotting factors and fibrinogen levels were perioperatively reduced, but platelet functions were less changed. Nomura et al[60]assessed the coagulation states after type A aortic dissection surgery and followed patients up for

82 months. In their study, hypercoagulability was identified even in the chronic phase, as measured by D-dimer and thrombin–antithrombin III complex. On the other hand, Li et al[61] studied patients with aortic dissection undergoing surgical repair and found that the relationship between the coagulation pathway and the postoperative inflammatory reaction should be considered in future studies. In this review, we were not able to explore any changes in blood parameters and inflammatory markers perioperatively, but we found a substantial need for blood product transfusion after surgery, suggesting the paramount effects of consumption coagulopathy on patients undergoing aortic surgeries. Further investigations about the coagulopathy-related factors and inflammatory markers could elucidate the proper application of such tests in the evaluation of patients undergoing the FET procedure for aortopathies.

The volume-outcome relationship associated with FET procedures is also worthy of discussion in the context of coagulopathy risk following FET. Mori et al. reported that lower-volume centres (fewer than 5 cases per year, reportedly making up 58.3% of centres) were at an increased risk of mortality (OR 2.50, 95% CI 2.08 - 3.01, $p < 0.0001$) compared to high-volume centres.[62] This is unsurprising as greater patient volume usually translates to more opportunities to practice intricate interventions. It has not been conclusively demonstrated that increased operating volume in FET repair translates to shorter CPB/HCA durations, but would it not be reasonable to suggest that, faced with the same patient, the more experienced surgeon would be able to accomplish the same standard of repair in a shorter duration than a novice surgeon? This would allow rewarming to occur earlier, and possibly therefore reducing the risk of coagulopathy risk in FET. The effect of longitudinal surgical training in FET implantation and device selection on postoperative outcomes could also be investigated – indeed, much research is required to substantiate this.

Despite the abundance of literature detailing the hemodynamic sequelae associated with aortic repair procedures - ranging from continued bleeding to impaired platelet function - any clinical correlation between coagulopathies and individual FET device characteristics hitherto remains to be elucidated.[63] In the present review we attempted to identify factors contributing to the development coagulopathy as well as sources of heterogeneity. Stent length, type, and surgical acuity were associated with a reduction in the heterogeneity of pooled estimate of reoperation for postoperative bleeding. In addition, in meta-regression analysis we found that both male and younger age were associated with a reduced risk of reoperation for postoperative bleeding.

No studies have evaluated predictors of coagulopathy among patients undergoing the FET procedure. Further investigations with a focus on finding predictors of bleeding and of coagulation events would be of great use to guide surgeons for risk stratification of patients scheduled for the FET procedure. For example, FET graft size and length is a well-known area of contention amongst aortic surgeons, and there currently exists no consensus around on the optimal approach to hybrid prosthesis sizing.[63]

Evidence on the effect of hybrid prosthesis sizing on clinical outcomes is varied – under-sizing has been reported as falling short of achieving an optimal seal, while over-sizing has been associated with further intimal injury and distal stent-induced entry tears with endoleak.[64] Because suboptimal graft sizing can potentially lead to endoleak, perhaps necessitating reintervention to address postoperative bleeding, graft sizing is a pertinent area for investigation as a potential predictor or risk factor of FET-associate coagulopathy. Indeed, there exists robust data on the relationship between neurological outcome and FET graft sizing. For example, Preventza et al. report that stent lengths below 10 cm carried a lower risk of SCI, and Tan et al. suggest that proximalisation of TAR to Zone 0 may be associated with improved neurological outcomes.[65, 66] Undoubtedly, a similarly nuanced appreciation of coagulopathy predictors associated with different FET devices and sizes would be of great benefit. This would facilitate a more holistic understanding of the risks and benefits associated with each individual procedure and allow a more nuanced evaluation of patient-specific needs and risks.

Apart from graft sizing, several FET devices are available,[67-71] and their usage in clinical practice is evolving so that studies for outcomes of such devices are being increased in literature.[51] The globally used tetrafurcate Thoraflex Hybrid®stent-graft provides separate reimplantation of supra-aortic vessels, an easier anastomosis to the distal aortic arch, and radio-opaque markers in the stented part.

In the subgroup analysis, we also found that Thoraflex® and Frozenix® had no heterogeneity compared to moderate heterogeneity depicted for the E-vita® and the Cronus® devices. However, it's imperative to elicit that the wide generalization and distribution of Thoraflex Hybrid across diverse population groups globally and in line with different ethnic population applicability in concurrent to the streamed analysis in this review potentially raises the standards that Thoraflex Hybrid is considered as the gold standard. The global availability and wide application coupled with the multiplicity of the Thoraflex Hybrid marketing prowess and in alignment to clinical and surgical need with single perfusion branch and multi branch configuration have been utilized by many aortovascular surgeons who operate under diverse healthcare systems and have been apprenticed and trained differently. Henceforth, undoubtedly this could potentially explain the elicited heterogeneity of this device and its coagulopathy correlative outcomes as perceived comparatively to others FET including the Frozenix® and Cronus®.

Our analysis also revealed that the rate of reoperation for postoperative bleeding was the lowest the Thoraflex Hybrid® and for the Frozenix® among studies included in our proportional meta-analysis. Bearing these findings in mind it is worth highlighting that in a systematic review comparing the Thoraflex Hybrid® and E-vita® devices, Harky et al. emphasized that Thoraflex Hybrid® is more frequently implanted in cases of emergent aortic repair than E-vita®. Notwithstanding the effect of baseline patient demographics on clinical outcomes, this supports our finding that Thoraflex Hybrid® was associated with lower rates of coagulopathy than E-vita, with minimal heterogeneity.[72] On the other hand, a recent report noted excessive oozing through the fabric of stent in three patients implanted the branched Cryolife-Jotec E-vita open NEO hybrid prosthesis.[73] The E-vita open Neo HP has been described as having a propensity for excessive oozing through its polyester wall, which lacks gelatin or collagen (a key component of preventing graft porosity). This significant limitation has been associated with poor postoperative outlook, and Czerny et al. describe one such patient requiring 23 U of RBC, 28 U of FFP, and 16 U of thrombocytes in the 24 hours following surgery. The postoperative courses of the patients affected by this porosity were complicated by factors including low cardiac output necessitating inotropes, haemodialysis, mutli-organ failure, paraplegia, and death.[73]

Though Jakob et al. argue that strategic employment of ROTEM may help deal with the graft's porosity, it is imperative to clinically point out that such an approach to FET-associated coagulopathy has been tested only on a small number of EVITA Neo, and no other FET devices.[74]

The heterogeneity of coagulopathy rates associated with the Cronus® and the E-vita® might be attributed to the diverse patient demographics (e.g., ethnicity) among studies reporting outcomes from E-vita® and because many such studies failed to report the major factors causing complications, rather than extracted variables in our meta-analysis.

Limitations

Main limitation for this systematic review and meta-analysis was the low rate of reporting variables related to the coagulopathy and blood products transfusion. Moreover, no studies highlighted causes of bleeding events in their respective population cohort, focusing on mere reporting number of cases without confounding factors. As long as head-to-head comparisons are lacking in this setting and the major shortages of reporting in some studies, we were unable to properly elucidate associated factors for FET-related coagulopathies.

Conclusion

This systematic review demonstrated an association between the FET procedure for total arch replacement and perioperative coagulopathy, as represented by a need for reoperation for bleeding and blood product transfusion. Being male and of a younger age were identified as being protective against these complications. Subgroup analysis revealed coagulopathy associated with Thoraflex® Hybrid and Frozenix® was not heterogenous, while that of E-vita® and Cronus® were subject to substantial heterogeneities in reporting. However, it is worth deducing that while Thoraflex Hybrid being used on a global scale and challenged by different clinical indications (aneurysm and dissections (acute and chronic), and in accordance to its apparent versatile performance, the outcomes of the device indicate consistent and superior non-heterogenicity in comparison to other available FET products in current surgical trend. Further investigation into the effect of various graft-specific characteristics, such as sizing, and human factors such as volume-outcome relationship on rates of perioperative coagulopathy are warranted.

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None

Conflict of interest

There were none to declare.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created in this study.

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Figure legends

Figure 1- PRISMA flow chart for finding articles

Figure 2- Pooled estimation of patients requiring reoperation for postoperative bleeding

Figure 3- Pooled estimation of patients with postoperative bleeding

Figure 4- Comparing pooled estimation of reoperation for postoperative bleeding in groups by the stent length size

Figure 5- Comparing pooled estimation of reoperation for postoperative bleeding in groups by the stent type

Figure 6- Comparing pooled estimation of reoperation for postoperative bleeding in groups by the male predominance

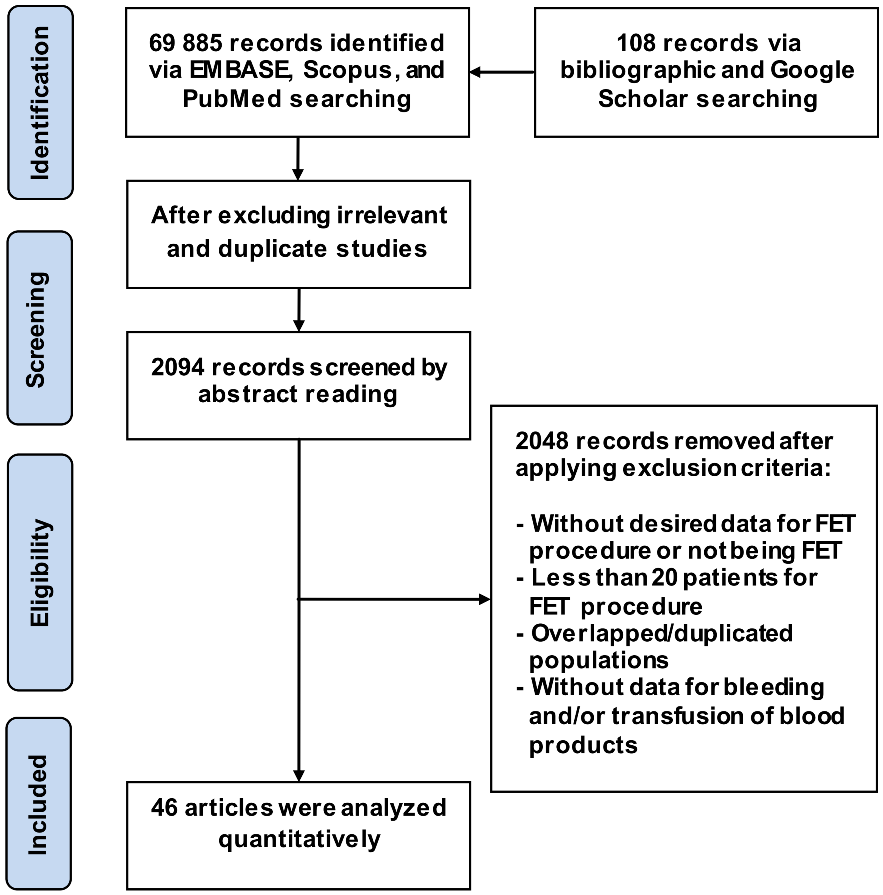
Figure 7- Comparing pooled estimation of reoperation for postoperative bleeding in groups by the operation chronicity

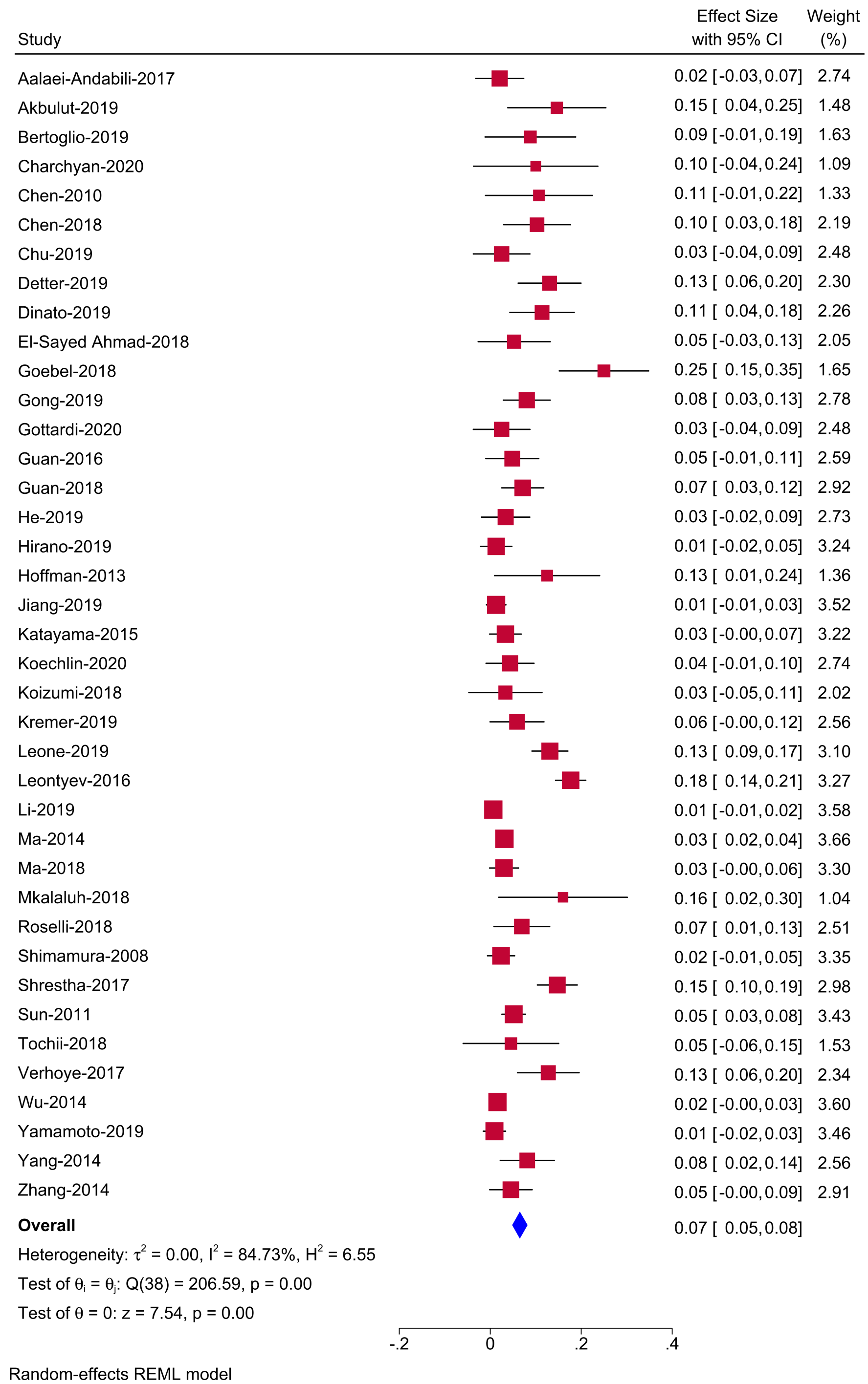
Figure 8- Bubble plot showing the association between hypothermic circulatory arrest duration and reoperation for postoperative bleeding

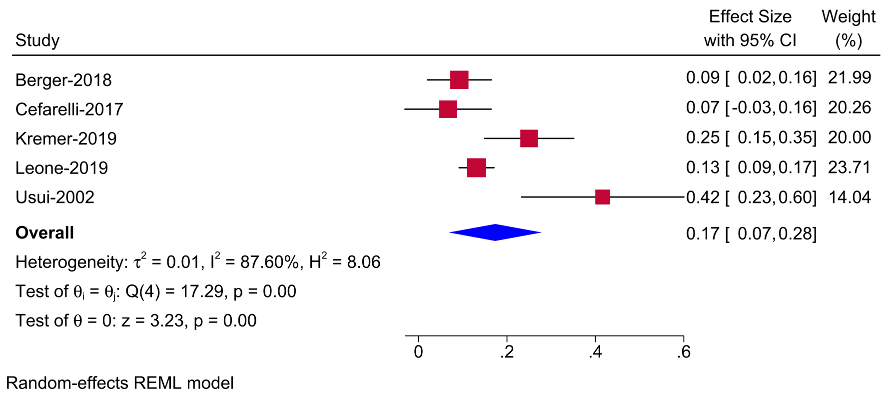
Supplementary Figure 1- Pooled estimation of patients with in-hospital mortality

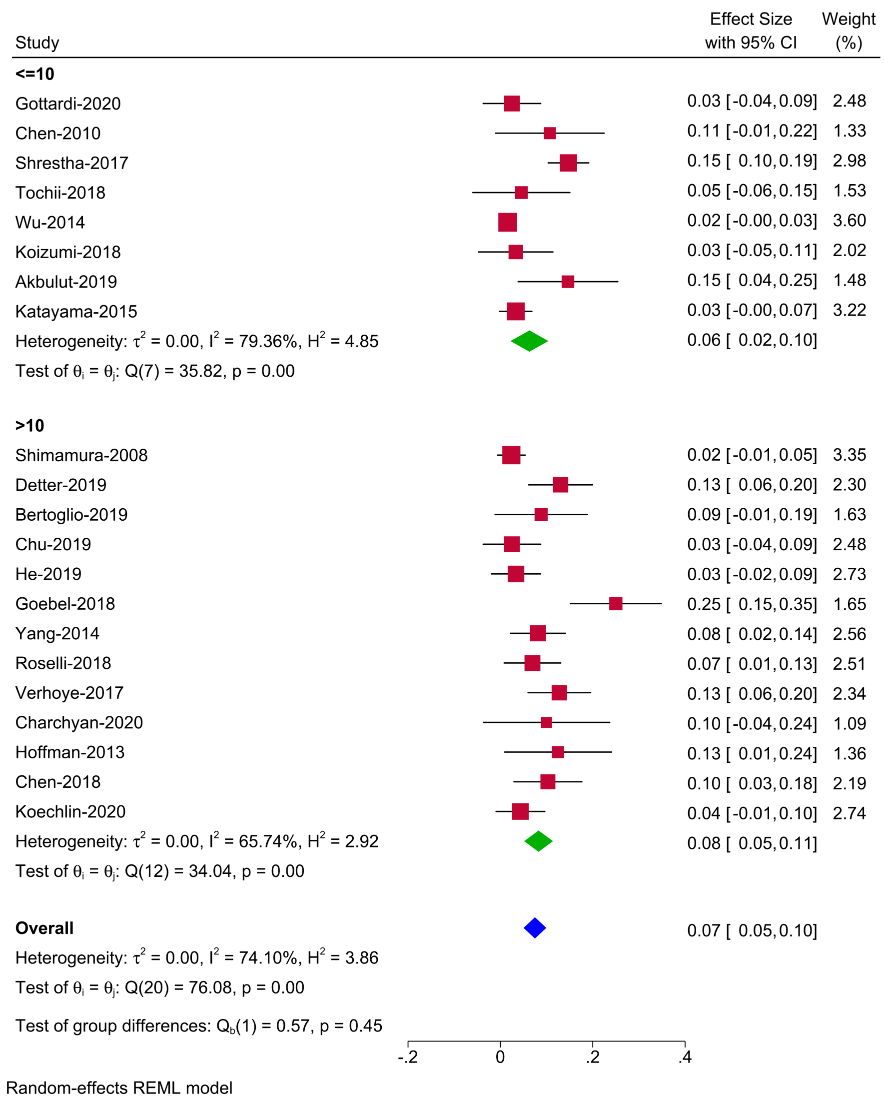
Supplementary Figure 2- Comparing pooled estimation of in-hospital mortality by (A) the stent length size and (B) the operation chronicity

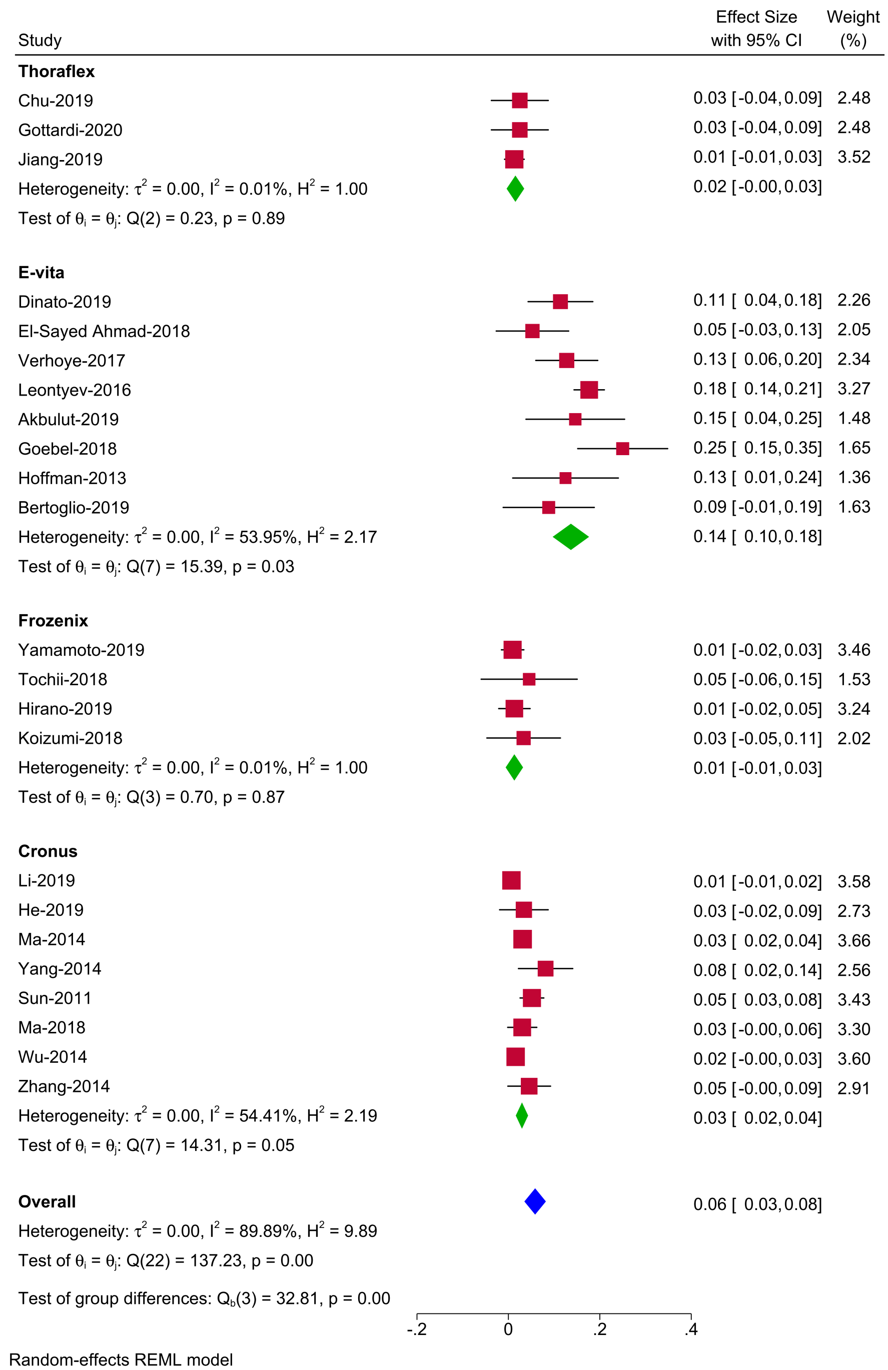
Supplementary Figure 3- Funnel plots showing publication bias for (A) reoperation for postoperative bleeding, (B) patients with postoperative bleeding, and (C) in-hospital mortality


Identification
Screening
Eligibility
Included
69 885 records identified via EMBASE, Scopus, and PubMed searching
108 records via bibliographic and Google Scholar searching
After excluding irrelevant and duplicate studies
2094 records screened by abstract reading
2048 records removed after applying exclusion criteria:
- Without desired data for FET procedure or not being FET
- Less than 20 patients for FET procedure
- Overlapped/duplicated populations
- Without data for bleeding and/or transfusion of blood products
46 articles were analyzed quantitatively

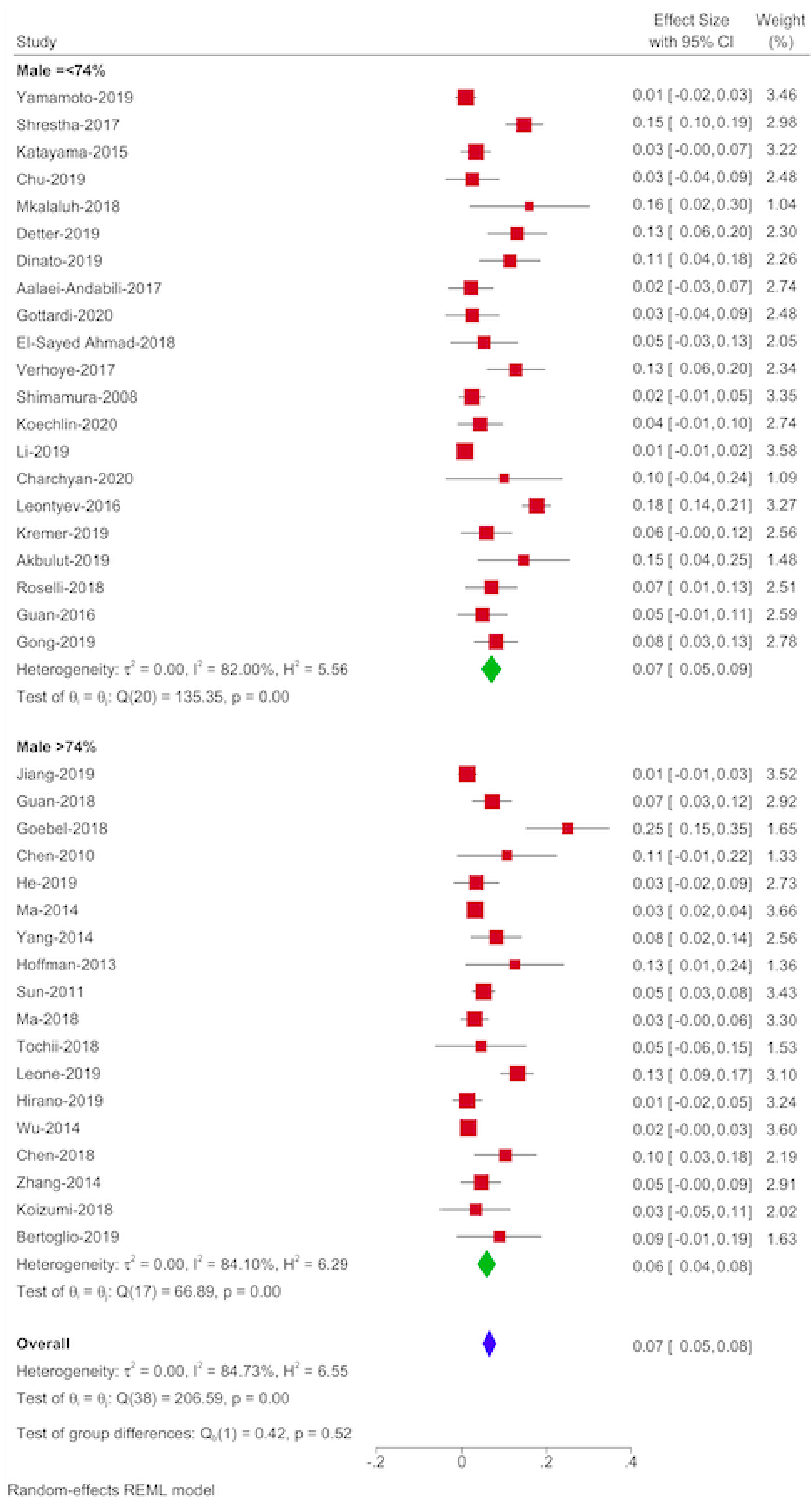

Study
Effect Size with 95% CI
Weight (%)
Aalaei-Andabili-2017 0.02 [-0.03, 0.07] 2.74
Akbulut-2019 0.15 [0.04, 0.25] 1.48
Bertoglio-2019 0.09 [-0.01, 0.19] 1.63
Charchyan-2020 0.10 [-0.04, 0.24] 1.09
Chen-2010 0.11 [-0.01, 0.22] 1.33
Chen-2018 0.10 [0.03, 0.18] 2.19
Chu-2019 0.03 [-0.04, 0.09] 2.48
Detter-2019 0.13 [0.06, 0.20] 2.30
Dinato-2019 0.11 [0.04, 0.18] 2.26
El-Sayed Ahmad-2018 0.05 [-0.03, 0.13] 2.05
Goebel-2018 0.25 [0.15, 0.35] 1.65
Gong-2019 0.08 [0.03, 0.13] 2.78
Gottardi-2020 0.03 [-0.04, 0.09] 2.48
Guan-2016 0.05 [-0.01, 0.11] 2.59
Guan-2018 0.07 [0.03, 0.12] 2.92
He-2019 0.03 [-0.02, 0.09] 2.73
Hirano-2019 0.01 [-0.02, 0.05] 3.24
Hoffman-2013 0.13 [0.01, 0.24] 1.36
Jiang-2019 0.01 [-0.01, 0.03] 3.52
Katayama-2015 0.03 [-0.00, 0.07] 3.22
Koechlin-2020 0.04 [-0.01, 0.10] 2.74
Koizumi-2018 0.03 [-0.05, 0.11] 2.02
Kremer-2019 0.06 [-0.00, 0.12] 2.56
Leone-2019 0.13 [0.09, 0.17] 3.10
Leontyev-2016 0.18 [0.14, 0.21] 3.27
Li-2019 0.01 [-0.01, 0.02] 3.58
Ma-2014 0.03 [0.02, 0.04] 3.66
Ma-2018 0.03 [-0.00, 0.06] 3.30
Mkalaluh-2018 0.16 [0.02, 0.30] 1.04
Roselli-2018 0.07 [0.01, 0.13] 2.51
Shimamura-2008 0.02 [-0.01, 0.05] 3.35
Shrestha-2017 0.15 [0.10, 0.19] 2.98
Sun-2011 0.05 [0.03, 0.08] 3.43
Tochii-2018 0.05 [-0.06, 0.15] 1.53
Verhoye-2017 0.13 [0.06, 0.20] 2.34
Wu-2014 0.02 [-0.00, 0.03] 3.60
Yamamoto-2019 0.01 [-0.02, 0.03] 3.46
Yang-2014 0.08 [0.02, 0.14] 2.56
Zhang-2014 0.05 [-0.00, 0.09] 2.91
Overall 0.07 [0.05, 0.08]
Heterogeneity: τ² = 0.00, I² = 84.73%, H² = 6.55
Test of θi = θj: Q(38) = 206.59, p = 0.00
Test of θ = 0: z = 7.54, p = 0.00
-.2
0
.2
.4
Random-effects REML model


Study
Effect Size with 95% CI
Weight (%)
Berger-2018 0.09 [0.02, 0.16] 21.99
Cefarelli-2017 0.07 [-0.03, 0.16] 20.26
Kremer-2019 0.25 [0.15, 0.35] 20.00
Leone-2019 0.13 [0.09, 0.17] 23.71
Usui-2002 0.42 [0.23, 0.60] 14.04
Overall 0.17 [0.07, 0.28]
Heterogeneity: τ² = 0.01, I² = 87.60%, H² = 8.06
Test of θi = θj: Q(4) = 17.29, p = 0.00
Test of θ = 0: z = 3.23, p = 0.00
0
.2
.4
.6
Random-effects REML model

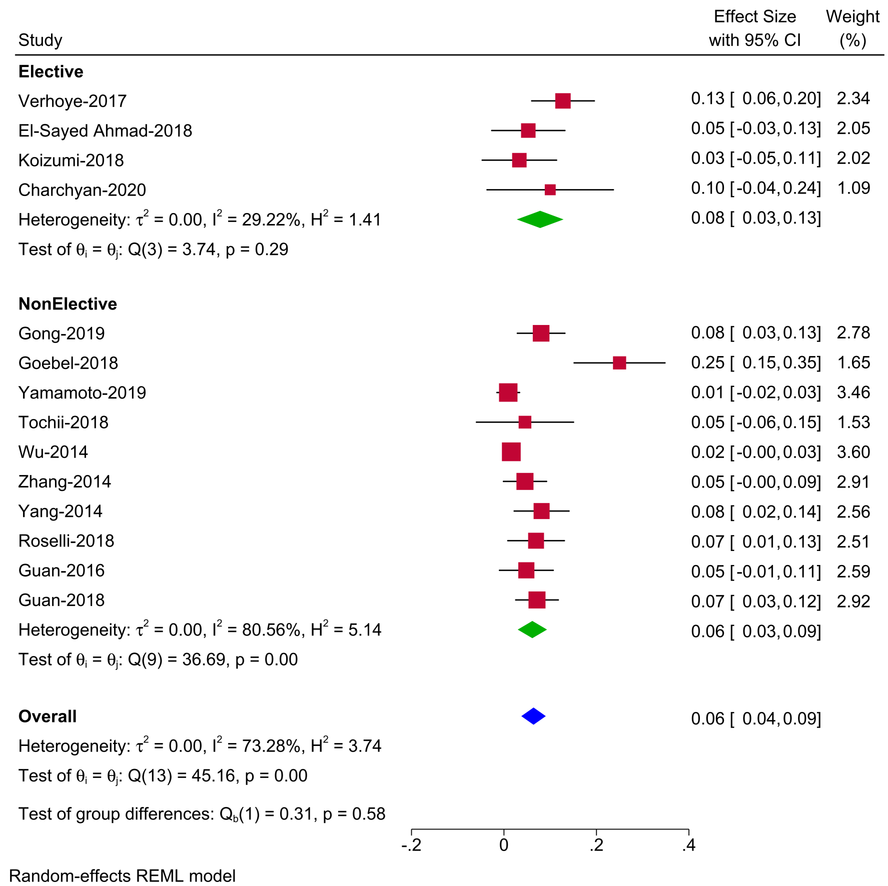

Study
Effect Size with 95% CI
Weight (%)
<=10
Gottardi-2020 0.03 [-0.04, 0.09] 2.48
Chen-2010 0.11 [-0.01, 0.22] 1.33
Shrestha-2017 0.15 [0.10, 0.19] 2.98
Tochii-2018 0.05 [-0.06, 0.15] 1.53
Wu-2014 0.02 [-0.00, 0.03] 3.60
Koizumi-2018 0.03 [-0.05, 0.11] 2.02
Akbulut-2019 0.15 [0.04, 0.25] 1.48
Katayama-2015 0.03 [-0.00, 0.07] 3.22
Heterogeneity: τ² = 0.00, I² = 79.36%, H² = 4.85 0.06 [0.02, 0.10]
Test of θi = θj: Q(7) = 35.82, p = 0.00
>10
Shimamura-2008 0.02 [-0.01, 0.05] 3.35
Detter-2019 0.13 [0.06, 0.20] 2.30
Bertoglio-2019 0.09 [-0.01, 0.19] 1.63
Chu-2019 0.03 [-0.04, 0.09] 2.48
He-2019 0.03 [-0.02, 0.09] 2.73
Goebel-2018 0.25 [0.15, 0.35] 1.65
Yang-2014 0.08 [0.02, 0.14] 2.56
Roselli-2018 0.07 [0.01, 0.13] 2.51
Verhoye-2017 0.13 [0.06, 0.20] 2.34
Charchyan-2020 0.10 [-0.04, 0.24] 1.09
Hoffman-2013 0.13 [0.01, 0.24] 1.36
Chen-2018 0.10 [0.03, 0.18] 2.19
Koechlin-2020 0.04 [-0.01, 0.10] 2.74
Heterogeneity: τ² = 0.00, I² = 65.74%, H² = 2.92 0.08 [0.05, 0.11]
Test of θi = θj: Q(12) = 34.04, p = 0.00
Overall 0.07 [0.05, 0.10]
Heterogeneity: τ² = 0.00, I² = 74.10%, H² = 3.86
Test of θi = θj: Q(20) = 76.08, p = 0.00
Test of group differences: Qb(1) = 0.57, p = 0.45
-.2
0
.2
.4
Random-effects REML model

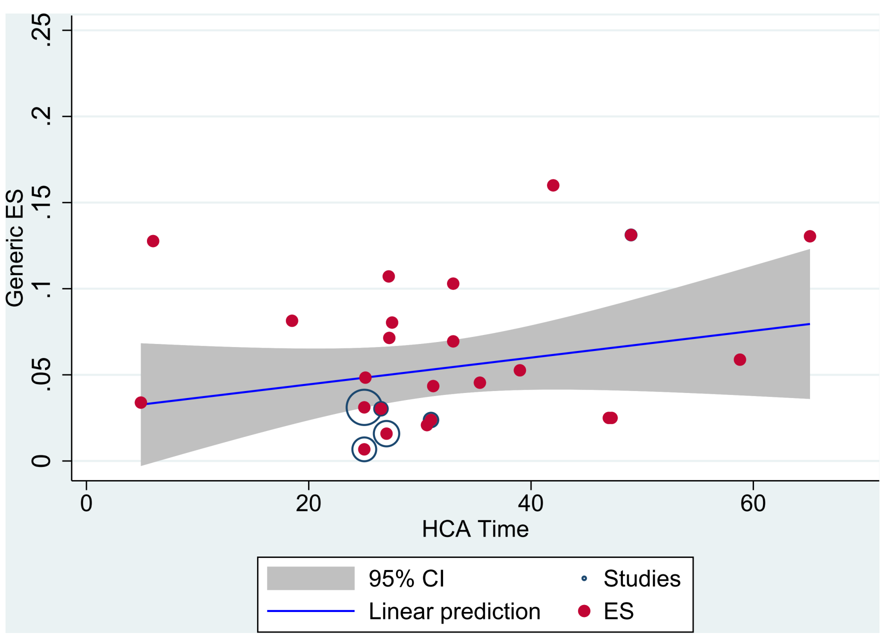


Study
Effect Size with 95% CI
Weight (%)
Thoraflex
Chu-2019 0.03 [-0.04, 0.09] 2.48
Gottardi-2020 0.03 [-0.04, 0.09] 2.48
Jiang-2019 0.01 [-0.01, 0.03] 3.52
Heterogeneity: τ² = 0.00, I² = 0.01%, H² = 1.00 0.02 [-0.00, 0.03]
Test of θi = θj: Q(2) = 0.23, p = 0.89
E-vita
Dinato-2019 0.11 [0.04, 0.18] 2.26
El-Sayed Ahmad-2018 0.05 [-0.03, 0.13] 2.05
Verhoye-2017 0.13 [0.06, 0.20] 2.34
Leontyev-2016 0.18 [0.14, 0.21] 3.27
Akbulut-2019 0.15 [0.04, 0.25] 1.48
Goebel-2018 0.25 [0.15, 0.35] 1.65
Hoffman-2013 0.13 [0.01, 0.24] 1.36
Bertoglio-2019 0.09 [-0.01, 0.19] 1.63
Heterogeneity: τ² = 0.00, I² = 53.95%, H² = 2.17 0.14 [0.10, 0.18]
Test of θi = θj: Q(7) = 15.39, p = 0.03
Frozenix
Yamamoto-2019 0.01 [-0.02, 0.03] 3.46
Tochii-2018 0.05 [-0.06, 0.15] 1.53
Hirano-2019 0.01 [-0.02, 0.05] 3.24
Koizumi-2018 0.03 [-0.05, 0.11] 2.02
Heterogeneity: τ² = 0.00, I² = 0.01%, H² = 1.00 0.01 [-0.01, 0.03]
Test of θi = θj: Q(3) = 0.70, p = 0.87
Cronus
Li-2019 0.01 [-0.01, 0.02] 3.58
He-2019 0.03 [-0.02, 0.09] 2.73
Ma-2014 0.03 [0.02, 0.04] 3.66
Yang-2014 0.08 [0.02, 0.14] 2.56
Sun-2011 0.05 [0.03, 0.08] 3.43
Ma-2018 0.03 [-0.00, 0.06] 3.30
Wu-2014 0.02 [-0.00, 0.03] 3.60
Zhang-2014 0.05 [-0.00, 0.09] 2.91
Heterogeneity: τ² = 0.00, I² = 54.41%, H² = 2.19 0.03 [0.02, 0.04]
Test of θi = θj: Q(7) = 14.31, p = 0.05
Overall 0.06 [0.03, 0.08]
Heterogeneity: τ² = 0.00, I² = 89.89%, H² = 9.89
Test of θi = θj: Q(22) = 137.23, p = 0.00
Test of group differences: Qb(3) = 32.81, p = 0.00
-.2
0
.2
.4
Random-effects REML model



Study
Effect Size with 95% CI
Weight (%)
Male =<74%
Yamamoto-2019 0.01 [-0.02, 0.03] 3.46
Shrestha-2017 0.15 [0.10, 0.19] 2.98
Katayama-2015 0.03 [-0.00, 0.07] 3.22
Chu-2019 0.03 [-0.04, 0.09] 2.48
Mkalaluh-2018 0.16 [0.02, 0.30] 1.04
Detter-2019 0.13 [0.06, 0.20] 2.30
Dinato-2019 0.11 [0.04, 0.18] 2.26
Aalaei-Andabili-2017 0.02 [-0.03, 0.07] 2.74
Gottardi-2020 0.03 [-0.04, 0.09] 2.48
El-Sayed Ahmad-2018 0.05 [-0.03, 0.13] 2.05
Verhoye-2017 0.13 [0.06, 0.20] 2.34
Shimamura-2008 0.02 [-0.01, 0.05] 3.35
Koechlin-2020 0.04 [-0.01, 0.10] 2.74
Li-2019 0.01 [-0.01, 0.02] 3.58
Charchyan-2020 0.10 [-0.04, 0.24] 1.09
Leontyev-2016 0.18 [0.14, 0.21] 3.27
Kremer-2019 0.06 [-0.00, 0.12] 2.56
Akbulut-2019 0.15 [0.04, 0.25] 1.48
Roselli-2018 0.07 [0.01, 0.13] 2.51
Guan-2016 0.05 [-0.01, 0.11] 2.59
Gong-2019 0.08 [0.03, 0.13] 2.78
Heterogeneity: τ^2 = 0.00, I^2 = 82.00%, H^2 = 5.56 0.07 [0.05, 0.09]
Test of $\theta_i = \theta_j$: Q(20) = 135.35, p = 0.00
Male >74%
Jiang-2019 0.01 [-0.01, 0.03] 3.52
Guan-2018 0.07 [0.03, 0.12] 2.92
Goebel-2018 0.25 [0.15, 0.35] 1.65
Chen-2010 0.11 [-0.01, 0.22] 1.33
He-2019 0.03 [-0.02, 0.09] 2.73
Ma-2014 0.03 [0.02, 0.04] 3.66
Yang-2014 0.08 [0.02, 0.14] 2.56
Hoffman-2013 0.13 [0.01, 0.24] 1.36
Sun-2011 0.05 [0.03, 0.08] 3.43
Ma-2018 0.03 [-0.00, 0.06] 3.30
Tochii-2018 0.05 [-0.06, 0.15] 1.53
Leone-2019 0.13 [0.09, 0.17] 3.10
Hirano-2019 0.01 [-0.02, 0.05] 3.24
Wu-2014 0.02 [-0.00, 0.03] 3.60
Chen-2018 0.10 [0.03, 0.18] 2.19
Zhang-2014 0.05 [-0.00, 0.09] 2.91
Koizumi-2018 0.03 [-0.05, 0.11] 2.02
Bertoglio-2019 0.09 [-0.01, 0.19] 1.63
Heterogeneity: τ^2 = 0.00, I^2 = 84.10%, H^2 = 6.29 0.06 [0.04, 0.08]
Test of $\theta_i = \theta_j$: Q(17) = 66.89, p = 0.00
Overall 0.07 [0.05, 0.08]
Heterogeneity: τ^2 = 0.00, I^2 = 84.73%, H^2 = 6.55
Test of $\theta_i = \theta_j$: Q(38) = 206.59, p = 0.00
Test of group differences: $Q_b(1)$ = 0.42, p = 0.52
-.2
0
.2
.4
Random-effects REML model


Study
Effect Size with 95% CI
Weight (%)
Elective
Verhoye-2017 0.13 [0.06, 0.20] 2.34
El-Sayed Ahmad-2018 0.05 [-0.03, 0.13] 2.05
Koizumi-2018 0.03 [-0.05, 0.11] 2.02
Charchyan-2020 0.10 [-0.04, 0.24] 1.09
Heterogeneity: τ² = 0.00, I² = 29.22%, H² = 1.41 0.08 [0.03, 0.13]
Test of θi = θj: Q(3) = 3.74, p = 0.29
NonElective
Gong-2019 0.08 [0.03, 0.13] 2.78
Goebel-2018 0.25 [0.15, 0.35] 1.65
Yamamoto-2019 0.01 [-0.02, 0.03] 3.46
Tochii-2018 0.05 [-0.06, 0.15] 1.53
Wu-2014 0.02 [-0.00, 0.03] 3.60
Zhang-2014 0.05 [-0.00, 0.09] 2.91
Yang-2014 0.08 [0.02, 0.14] 2.56
Roselli-2018 0.07 [0.01, 0.13] 2.51
Guan-2016 0.05 [-0.01, 0.11] 2.59
Guan-2018 0.07 [0.03, 0.12] 2.92
Heterogeneity: τ² = 0.00, I² = 80.56%, H² = 5.14 0.06 [0.03, 0.09]
Test of θi = θj: Q(9) = 36.69, p = 0.00
Overall 0.06 [0.04, 0.09]
Heterogeneity: τ² = 0.00, I² = 73.28%, H² = 3.74
Test of θi = θj: Q(13) = 45.16, p = 0.00
Test of group differences: Qb(1) = 0.31, p = 0.58
-.2
0
.2
.4
Random-effects REML model


Generic ES
0
.05
.1
.15
.2
.25
0
20
40
60
HCA Time
95% CI
Linear prediction
Studies
ES

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Tables.docx available at https://authorea.com/users/340497/articles/539070-correlation-of-coagulopathy-and-frozen-elephant-trunk-use-in-aortic-arch-surgery-a-systematic-review-and-meta-analysis

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Table 2.docx available at https://authorea.com/users/340497/articles/539070-correlation-of-coagulopathy-and-frozen-elephant-trunk-use-in-aortic-arch-surgery-a-systematic-review-and-meta-analysis

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Table 3.docx available at https://authorea.com/users/340497/articles/539070-correlation-of-coagulopathy-and-frozen-elephant-trunk-use-in-aortic-arch-surgery-a-systematic-review-and-meta-analysis