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Systematic Review

Does False Lumen Thrombosis Lead to Better Outcomes in Patients with Aortic Dissection: A Meta-Analysis and Systematic Review

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Abstract

Objectives: For a long time, the association of the false lumen status and the outcomes of patients suffering from aortic dissection has been unclear, so this review article aims to study whether the unobstructed of the false lumen is related to the outcome of patients suffering from aortic dissection. **Methods**: We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta Analyzes Protocols (PRISMA) statement 2009 and registered with PROSPERO (CRD42022381869). We searched PubMed, the Cochrane library, Web of Science and Embase to collect potential studies. The Newcastle-Ottawa Scale was used to assess the quality of the included studies. The main outcome is long-term survival. Data included in the study were summarized using the risk ratio or mean difference and 95% confidence interval. **Results**: There were 16 trials, 2829 patients in total, with a mean age of 62.1 years. Compared with completely thrombosed false lumen, patent group has better long-term survival (risk ratio (RR), 0.88; 95% CI, 0.79 to 0.97; $p = 0.01$; $I^2 = 58\%$) and smaller yearly aortic growth rate (mean difference (MD), 1.03; 95% CI, 0.23 to 1.82; $p = 0.01$; $I^2 = 98\%$). In addition, patients with a patent false lumen had a lower risk of aortic event (RR, 0.81; 95% CI, 0.68 to 0.97; $p = 0.02$; $I^2 = 37\%$), but higher risk of aortic rupture (RR, 7.02; 95% CI, 2.55 to 19.3; $p = 0.0002$; $I^2 = 0$) and hospital death (RR, 2.72; 95% CI, 1.45 to 5.08; $p = 0.002$; $I^2 = 0$). **Conclusion**: Completely thrombosed of the false lumen is more beneficial to the long-term survival of patients with aortic dissection. And the risk of aortic rupture and hospital death in patients with patent false lumen is 7 times and 3 times that of patients with complete thrombosed false lumen. It is expected to provide individualized medical care for different types of patients according to different false lumen status to minimize death and related complications.

Keywords

aortic dissection; prognosis; false lumen; meta-analysis

Introduction

Aortic dissection (AD) is usually an acute, fatal syndrome of sudden chest pain caused by a tear in the intima and media of vessel. Immediate diagnosis and appropriate interventions are essential for AD patients. At present, computed tomography angiography has become the gold standard for diagnosing AD, and there are many options for treatment. Although all these methods have saved many acute AD patients, the mortality rate of AD patients is still about 20% [1]. That is to say, although timely medical intervention can reduce the short-term mortality of AD to a certain extent, we need to pay more attention to the postoperative state to improve the long-term survival rate of AD patients.

Several studies have shown that advanced age, female sex, history of atherosclerosis, and renal insufficiency are predictors of acute AD morbidity and mortality, but they are less specific and less convenient for assessing long-term clinical outcomes of patients [2–7]. Several trials have shown that false lumen status is linked with long-term prognosis in AD patients, but this view is still controversial. Some studies believe that the unobstructed false lumen is not conducive to the prognosis of patients, while complete blood clot of the false lumen leads to a better outcome [8,9]. It has also been suggested that false lumen unobstructed or thrombosis is not related to long-range mortality and the occurrence of interventions in AD patients [10,11].

At present, the association of the false lumen status and the outcomes of AD patients is still contradictory. There are few relevant studies, and conducting randomized controlled trials is difficult. We therefore carried out a systematic review and meta-analysis of observational studies to explain the relationship between false lumen status and long-term prognosis of AD patients.

Methods

This study has been registered on the International Prospective Systematic Reviews Registry database platform (CRD42022381869). We performed this systematic

review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement [12].

Data Sources and Search Strategy

We searched PubMed, the Cochrane library, Web of Science and Embase from January 1, 2000 to June 30, 2023 to collect studies compared the correlation between false lumen status to long-range outcomes in patients suffering from aortic dissection. The search terms are as follows: [(Thrombosis) OR (Thromboses) OR (Blood Clot) OR (false lumen)] AND [(Aneurysm, Dissecting) OR (Aortic Dissection) OR (Aortic Dissections)]. Citations of individual articles were also searched to identify additional studies for inclusion. Specific retrieval strategy are presented in word format in the **Supplementary Material**.

Selection Criteria

Two authors (WS and SL) independently read the titles and abstract to perform the initial screening. Then read the full text for a second screening. Disagreements were resolved through discussion with the third author (RL). All studies were observational studies reporting comparisons of false lumen patency and thrombosis. Inclusion criteria mainly include the following: (i) studies related to patients with aortic dissection and reporting the prognosis of false lumen in different states. (ii) The data can be used to incorporate the study's established outcomes. (iii) have long-term (at least one year) follow-up. Trials that meet one of the following conditions will be excluded: (i) Case reports, reference abstracts, letters, etc. (ii) Studies that did not state the outcomes of false lumen patency and false lumen thrombosis separately. (iii) No full-text study found.

Data Collection and Quality Evaluation

For each included literature, data extraction was carried out independently by two authors (SZ and BS) and reviewed by a third author (RL). The contents to extract include author's name, country, year of study, age, sex, sample size, Stanford classification, comorbidities (Marfan syndrome, hypertension), average follow-up time and outcome that need to be combined.

The quality evaluation of each included study was independently assessed by two writers (LX and SZ) using the Newcastle-Ottawa Scale (NOS), and any differences were resolved through discussion. Two authors evaluated the level of each included literature from the following aspects: selection bias, comparability bias, and exposure bias. The estimate is full of nine stars. All differences are resolved through discussion.

Outcomes and Definitions

We first compared outcomes related to completely patent and completely thrombosed, and then we compared outcomes related to patent and partially thrombosed. The primary outcome measure was long-term survival, mainly ten-year survival. Secondary outcomes include yearly aortic growth rate, aortic rupture, freedom from aortic event and hospital death to assess the outcomes of patients. The status of the false lumen was prospectively confirmed in each study based on imaging findings, including computed tomography or magnetic resonance imaging. Each study judged the state of the false lumen by experienced clinicians. For example, a patent false lumen was defined as no thrombus in the false lumen, complete thrombosis was defined as no contrast agent in the false lumen, and thrombosis in a partial lumen was defined as both thrombosis and contrast agent are present at the same time. Although the method for assessing false lumen status differed slightly from study to study, it was based on hemodynamics, so heterogeneity was minimal and acceptable.

Statistical Analysis

All data analyzes were obtained with Review Manager 5.4 (The Cochrane Collaboration, Copenhagen, Denmark) and Stata SE 16.0 (Stata Corporation, Texas, USA). The risk ratio (RR) and 95% confidence interval (CI) are used for the combination of dichotomic, and the mean difference (MD) with 95% CI is used for continuous variable. The size of heterogeneity is measured by I^2 test and Q test. When $p < 0.1$ or $I^2 > 50\%$, the results are considered to be highly heterogeneous and analyzed using random-effects model. When $I^2 < 50\%$, the results are considered to have moderate heterogeneity, and the fixed effects model is used for analysis. Subgroup analyzes and meta-regression were performed to explore potential sources of heterogeneity. When there were at least 8 studies, funnel plots, Begg's test and Egger's test were used to assess publication bias. Set the significance level $\alpha = 0.05$ for all analyses. Sensitivity analysis is used to test whether the results are robust and also to explore heterogeneity.

Results

Study Selection

We collected 380 trials from Pubmed, 155 trials from embase, 109 trials from Cochrane library, and 973 trials from the Web of Science. After excluding duplicates, 1460 trials participated in the primary screening at the title and abstract levels in total. After the initial screening, 50 trials were retained and downloaded to read the full text for screening. Ultimately, sixteen observational studies were

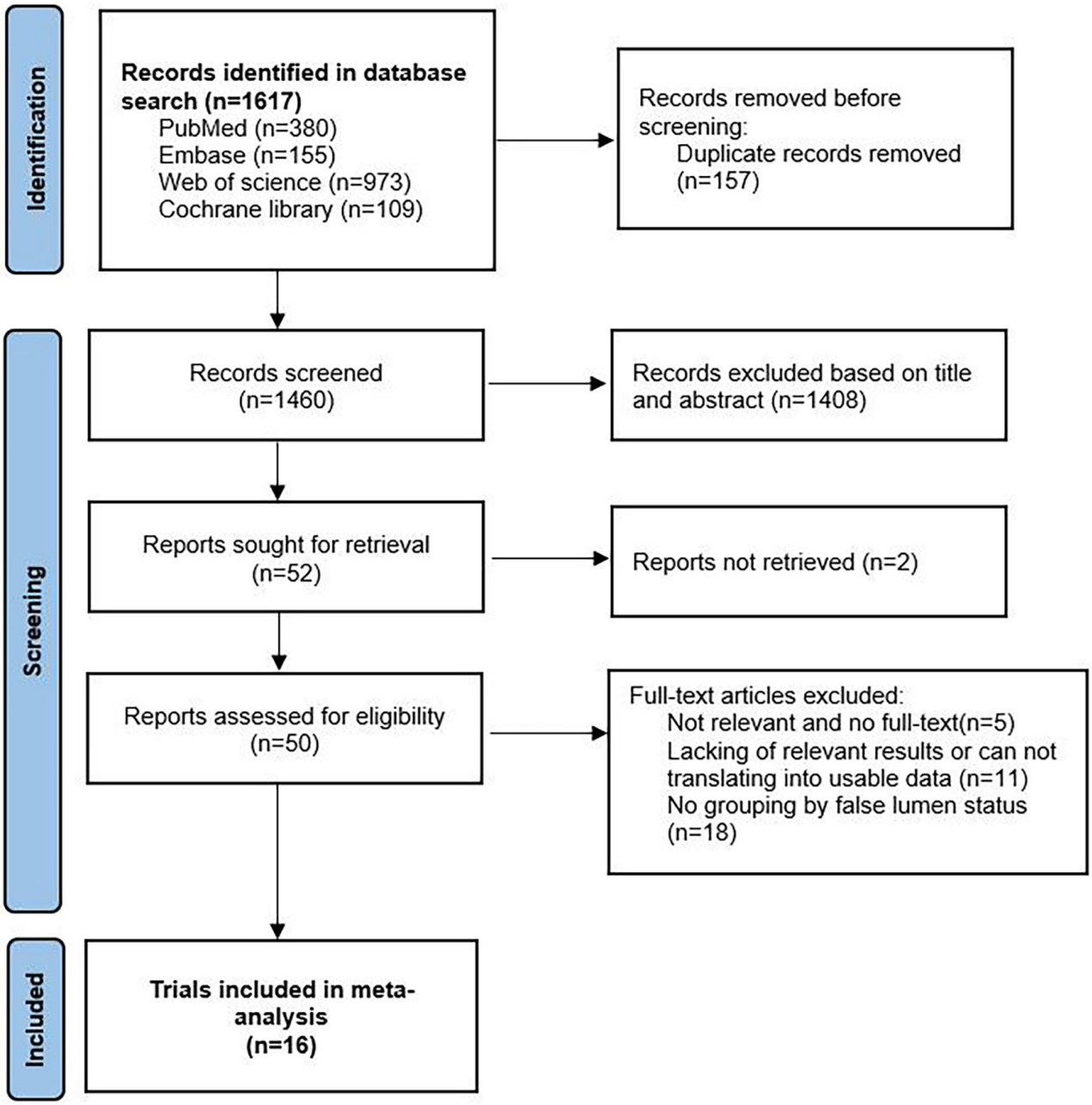

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

Table 1. Baseline characteristics of included studies for meta-analysis.

Reference	Country	Sample size	Age (years)	Male, %	Stanford classification	Marfan syndrome, %	Hypertension, %	Average follow-up (years)	NOS score
Akutsu 2004 [13]	Japan	110	63.5	64.5	B	NA	NA	5.5	8
Fattouch 2009 [14]	Italy	189	52.0	78.3	A	26.0	81.5	7.3	8
Kimura 2008 [15]	Japan	193	62.2	54.9	A	2.6	67.9	4.3	7
Kimura 2015 [8]	Japan	534	63.5	51.9	A	2.5	71.8	6.8	7
Kudo 2014 [16]	Japan	117	68.9	69.3	B	NA	82.9	5.1	7
Larsen 2013 [10]	Norway	522	57.9	74.9	A	5.8	70.9	5	6
Lin 2018 [17]	China	70	55.6	72.4	A	NA	81.0	NA	7
Miyahara 2011 [18]	Japan	160	66.1	76.9	B	NA	34.4	3.7	7
Song 2010 [19]	Korea	118	60.0	55.0	A	NA	NA	3.5	8
Sueyoshi 2009 [20]	Japan	71	64.4	69.0	B	NA	74.6	4.1	7
Tanaka 2014 [21]	Japan	103	67.1	67.0	B	NA	87.4	3.1	8
Tanaka 2017 [22]	Japan	62	73.0	46.8	A	3.2	83.9	NA	8
Trimarchi 2013 [23]	Italy	84	NA	NA	B	NA	NA	2.2	7
Tsai 2007 [24]	Germany	201	60.8	69.2	B	5.5	77.0	2.8	8
Tsai 2014 [25]	China	67	53.0	74.6	A	NA	73.1	6.28	8
Ueki 2014 [26]	Japan	228	70.4	67.1	B	0.9	NA	3.2	7

NOS, Newcastle-Ottawa Scale; NA, not available. Value are expressed as mean.

included and participated in this study [8,10,13–26]. The specific screening process and reasons are shown in Fig. 1.

Characteristics and Quality Evaluation

We extracted the baseline data of 16 included literature, and the details are shown in Table 1 (Ref. [8,10,13–26]). The trials were issued between 2004 and 2018. The sample volume of a single trial varied from 62 to 534. 2829 patients with aortic dissection participated in this meta-analysis in total, with a mean age of 62.1 years.

After quality evaluation, we found that the NOS quality evaluation results of the included studies were all at an upper-middle level, with scores greater than five stars, eligible for inclusion criteria in the meta-analysis. The ultimate scores are displayed in Table 1, and the detailed scores are shown in the **Supplementary Material**.

Main Outcomes of Study Results

There are eleven studies reported the long-term survival of patients with patent false lumen and completely thrombosed. Patients with a completely thrombosed false lumen had significantly better long-range survival compared with patients in patent group (Fig. 2A; RR, 0.88; 95% CI, 0.79 to 0.97; $p = 0.01$; $I^2 = 58\%$). We also compared the long-range survival of patients suffering from patent false lumen and partially thrombosed gruop in 6 reports. The results continued to suggest that patent status of the false lumen was worse to patients' long-term survival, although this result was not statistically significant (Fig. 2B; RR, 0.93; 95% CI, 0.85 to 1.02; $p = 0.11$; $I^2 = 0$).

In addition, we also analyzed the yearly aortic growth rate of patients with patent false lumen and completely thrombosed and partially thrombosed group. The results showed that the yearly aortic growth rate of patients with completely thrombosed was smaller than that of patients with patent false lumen group (Fig. 3A; MD, 1.03; 95%CI, 0.23 to 1.82; $p = 0.01$; $I^2 = 98\%$), and the yearly aortic growth rate of patients suffering from patent false lumen was lower than that of patients suffering from partially thrombosed group (Fig. 3B; MD, –0.19; 95% CI, –0.35 to –0.03; $p = 0.02$; $I^2 = 33\%$).

Finally, we analyzed freedom from aortic event, aortic rupture and hospital death in patients with patent false lumen and patients with completely thrombosed. The results indicated that patients suffering from a completely thrombosed false lumen owned a lower danger of aortic event (Fig. 4A; RR, 0.81; 95% CI, 0.68 to 0.97; $p = 0.02$; $I^2 = 37\%$), aortic rupture (Fig. 4B; RR, 7.02; 95% CI, 2.55 to 19.3; $p = 0.0002$; $I^2 = 0$) and hospital death (Fig. 4C; RR, 2.72; 95% CI, 1.45 to 5.08; $p = 0.002$; $I^2 = 0$).

Subgroup Analysis

Subgroup analysis of long-term survival and yearly aortic growth rate were performed according to different Stanford classifications. The results showed that the opening of the false lumen was not conducive to the long-term survival of patients in either Stanford type A or B patients, and there was no significant difference in risk between type A and B patients (Fig. 5). For the yearly aortic growth rate, regardless of Stanford type A or B patients, the complete thrombosis of false lumen has a smaller annual aortic growth rate, and the yearly aortic growth rate of B type patients is smaller than that of A type (Fig. 6). In addition, different Stanford classifications are not the main source of heterogeneity in long-term survival and yearly aortic growth rate. Subgroup analysis of long-term survival of patients in different age groups shows that age was one of the sources of heterogeneity in long-term survival (Fig. 7). Subgroup analysis of long-term survival of patients whether surgery or not shows that surgical treatment was not a source of heterogeneity and was not a relevant confounder (Fig. 8).

Meta-Regression

Sample size, age, male sex, hypertension, and follow-up time were included in random-effects univariate meta-regression analyzes of long-term survival and yearly aortic growth rate. The results show that none of the above covariates is the main source of heterogeneity in long-term survival and yearly aortic growth rate. Specific results are presented in the **Supplementary Material**.

Publication Bias Evaluation and Sensitivity Analysis

The funnel plots of long-term survival and yearly aortic growth rate are basically symmetrical, and the funnel plots are shown in the **Supplementary Material**. We also performed begg's test and egger's test on long-term survival (Egger's $p = 0.397$; Begg's $p = 0.755$) and yearly aortic growth rate (Egger's $p = 0.921$; Begg's $p = 0.602$). For other outcomes, the assessment of publication bias was not conducted because the number of included literatures was less than eight. Results of assessments of publication bias are presented in the **Supplementary Material**. Sensitivity analysis indicated that the results were reliable and robust, and the study by Fattouch *et al.* [14]. may be one of the sources of heterogeneity in yearly aortic growth rate.

Discussion

AD is an extremely dangerous disease with acute onset, rapid disease progression, and high mortality, especially acute AD, which not only has poor outcomes, but also brings a huge burden of disease to patients [27]. In re-

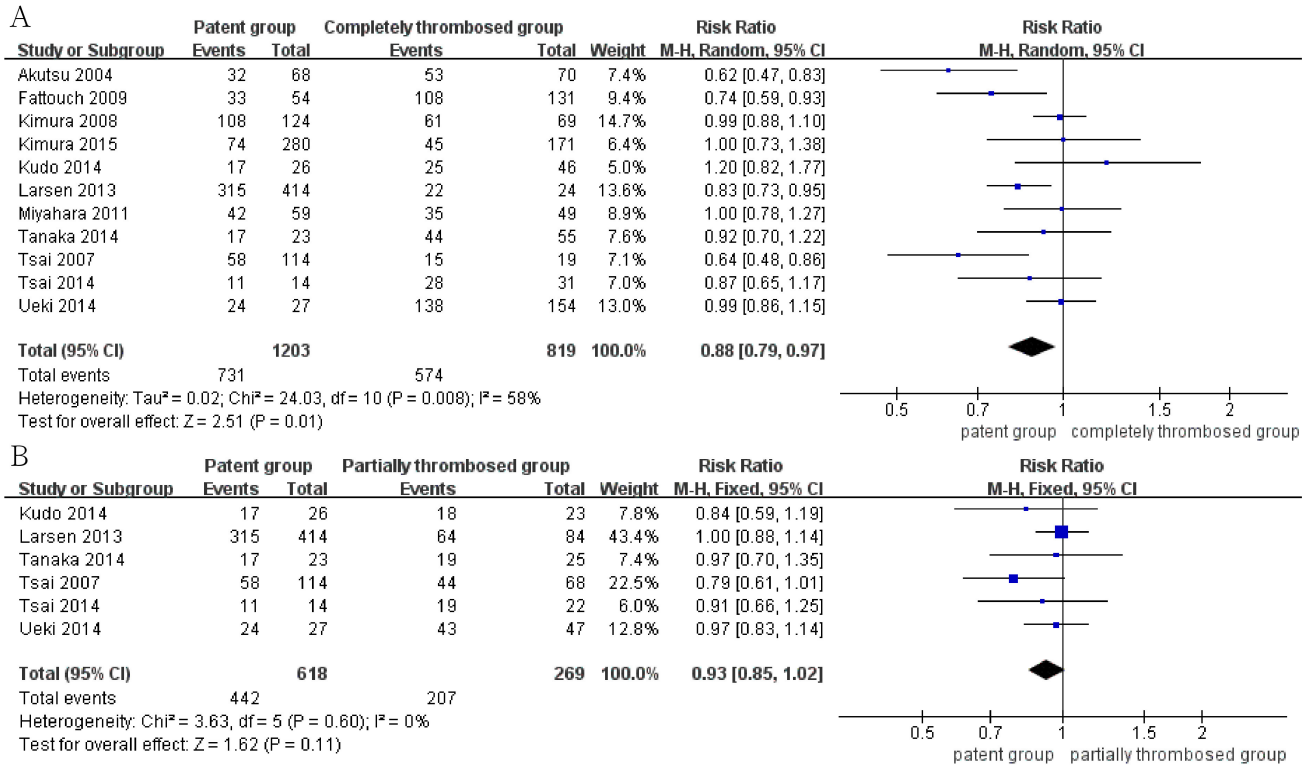

Fig. 2. Forest plot of (A) long-term survival between patent and completely thrombosed group; (B) long-term survival between patent and partially thrombosed group.

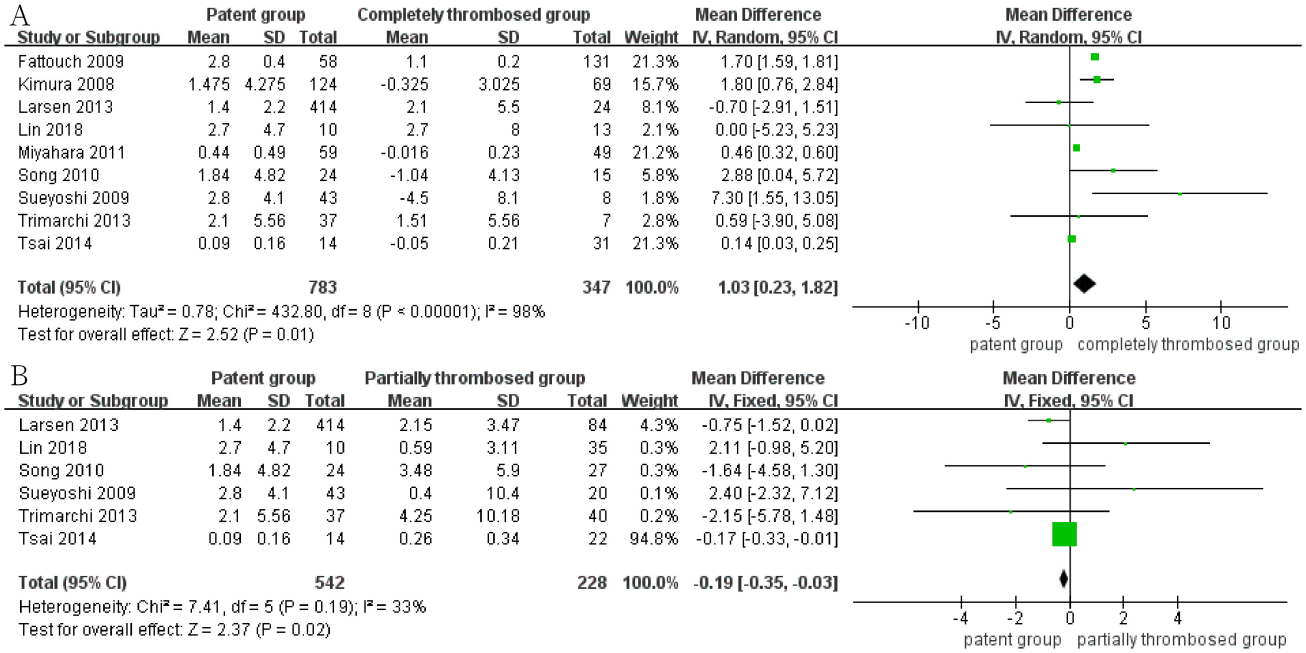

Fig. 3. Forest plot of (A) yearly aortic growth rate between patent and completely thrombosed group; (B) yearly aortic growth rate between patent and partially thrombosed group.

cent years, the relationship between false lumen status and the outcomes of patients with acute AD has been paid more and more attention, although there are relatively few related studies. We therefore performed this systematic review and meta-analysis of observational studies to further explore the relationship between them. Conventional wisdom holds that complete thrombus formation prevents blood from entering the dissection further, thereby reducing the pressure

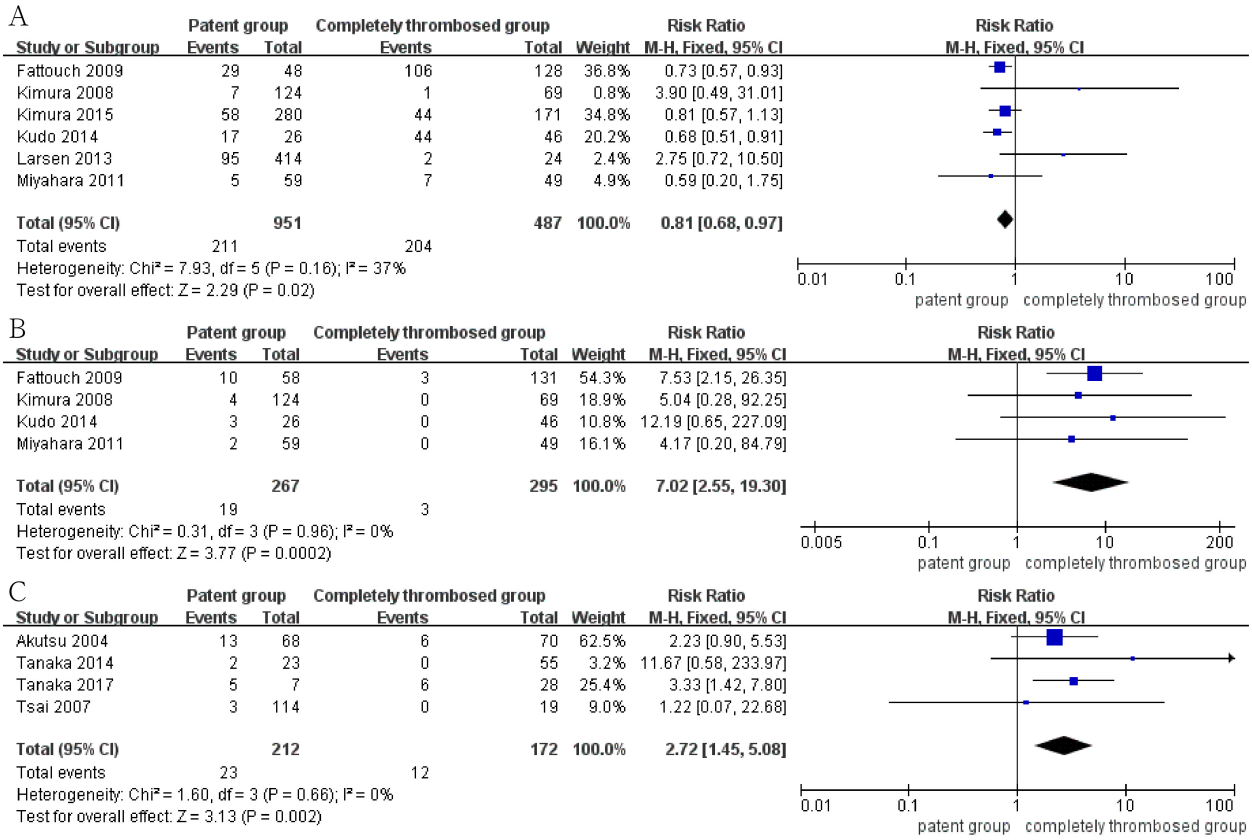

Fig. 4. Forest plot of (A) freedom from aortic event; (B) aortic rupture; (C) hospital death between patent and completely thrombosed group.

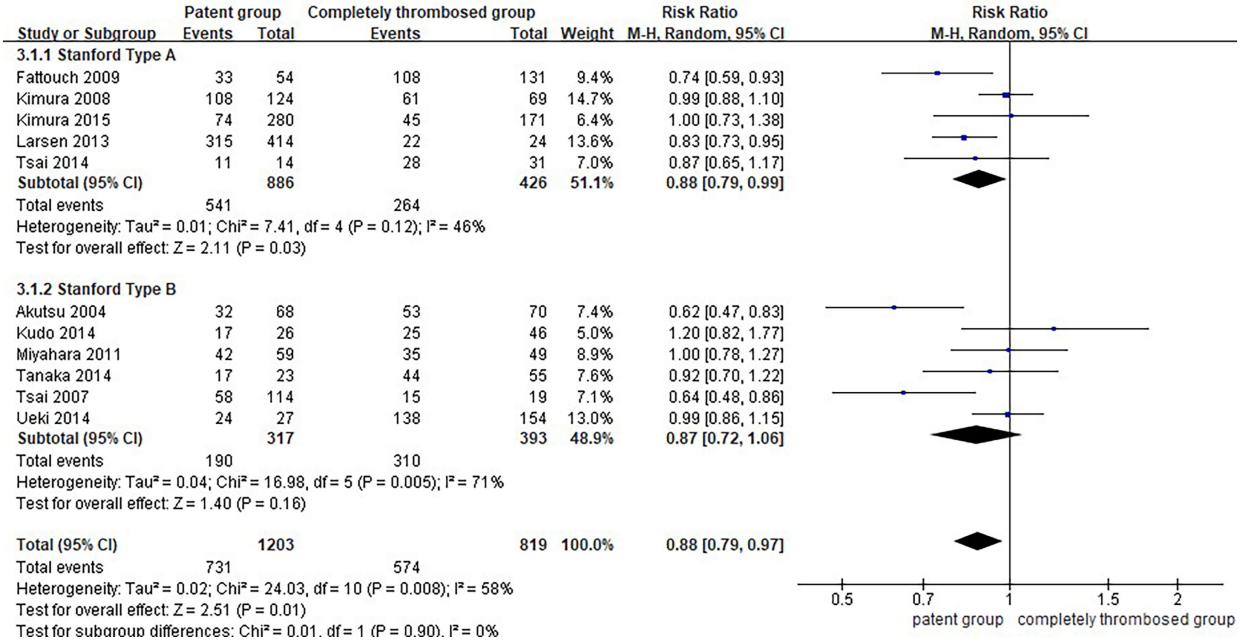

Fig. 5. Subgroup analysis of different Stanford classifications on long-term survival.

in the dissection cavity and reducing the risk of dissection expansion and rupture. Thrombosis may also help stabilize entrapment and reduce hemodynamic instability. Therefore, patients with complete thrombosis must have a better prognosis. However, other studies have reported that complete false lumen thrombosis does not affect long-term mortality, reintervention rates, or aortic growth [10,16].

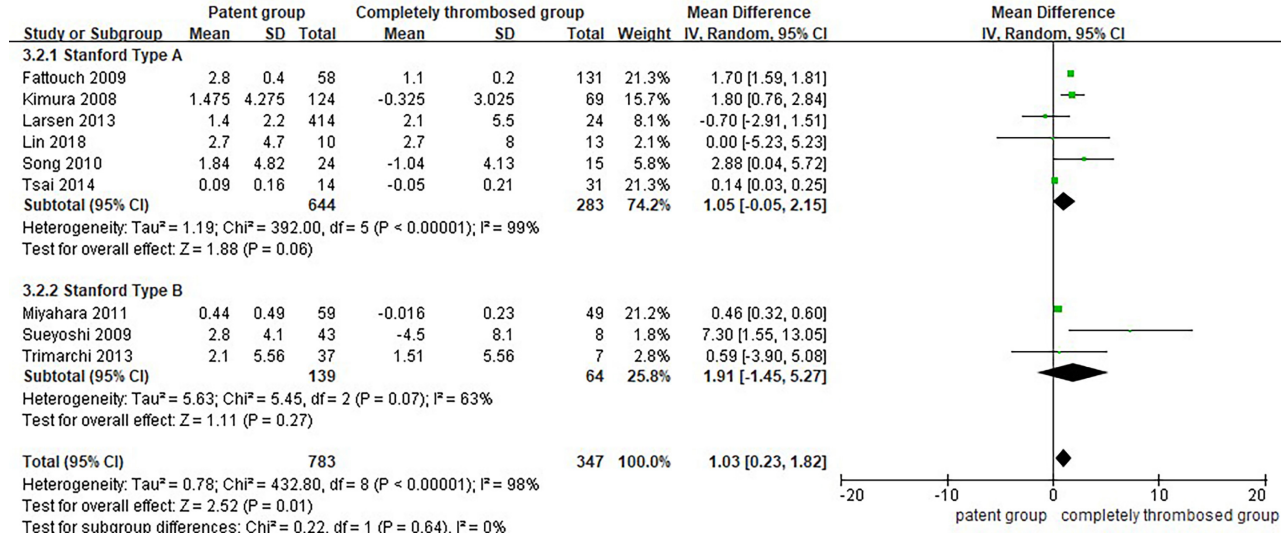

Fig. 6. Subgroup analysis of different Stanford classifications on yearly aortic growth rate.

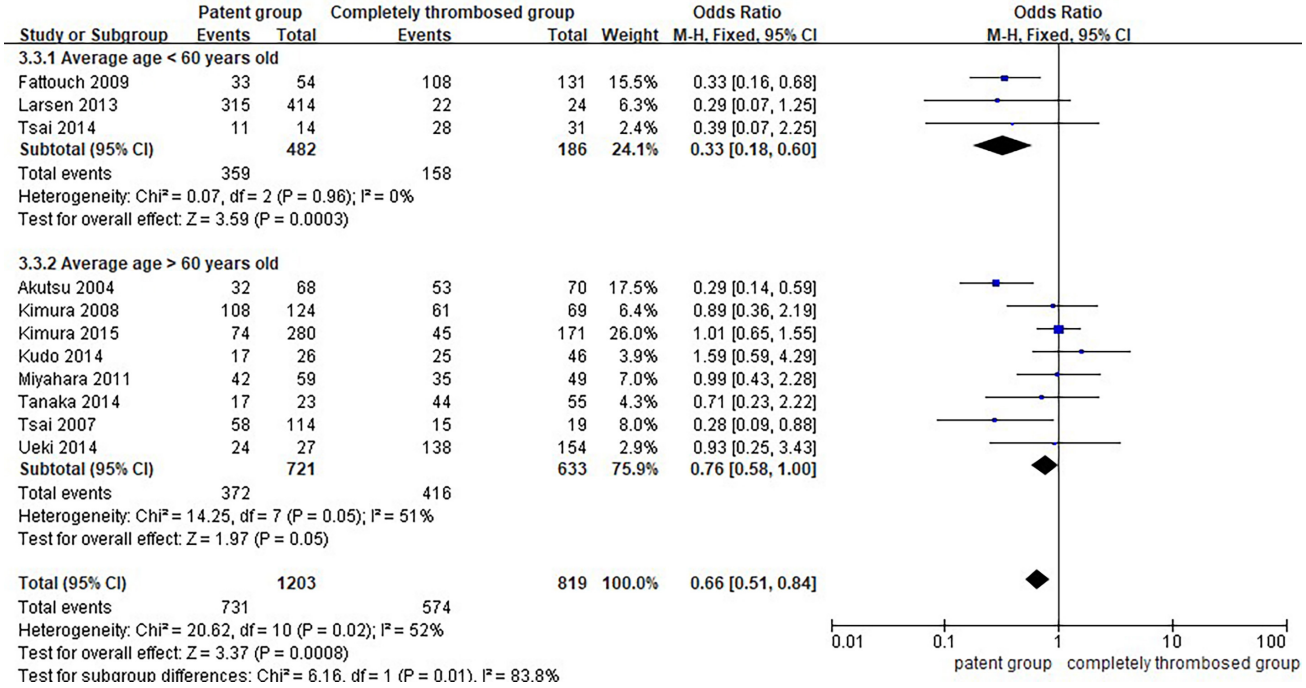

Fig. 7. Subgroup analysis of long-term survival of patients in different age groups.

This study included 16 studies, and the results showed that patients with completely thrombosed false lumen had better outcomes and long-term survival. Patients with a completely thrombosed false lumen as well as those with a partially thrombosed false lumen had better long-term survival, whereas patients with a completely patent false lumen had the worst long-term survival. Yearly aortic growth rate is a measure of aortic dilatation, and compared with completely thrombosed and partially thrombosed, the completely patent group had a smaller yearly aortic growth rate. As for aortic event, aortic rupture and hospital death, patients with completely thrombosed also have a lower risk. Although the RR of this result may be inflated due to sample limitations, it is not impressed by the positive result itself. In addition, the results of the subgroup analysis indicated that in terms of long-term survival, there was no statistically significant difference between different Stanford types, but Stanford type B had a smaller yearly aortic growth rate. Regarding heterogeneity, we adopted subgroup analysis, meta-regression and sensitivity analysis to explore the source of heterogeneity. Subgroup analysis suggests that one of the main potential sources of heterogeneity in long-term survival outcomes is age. For the yearly aortic growth rate, it is measured and calculated based on

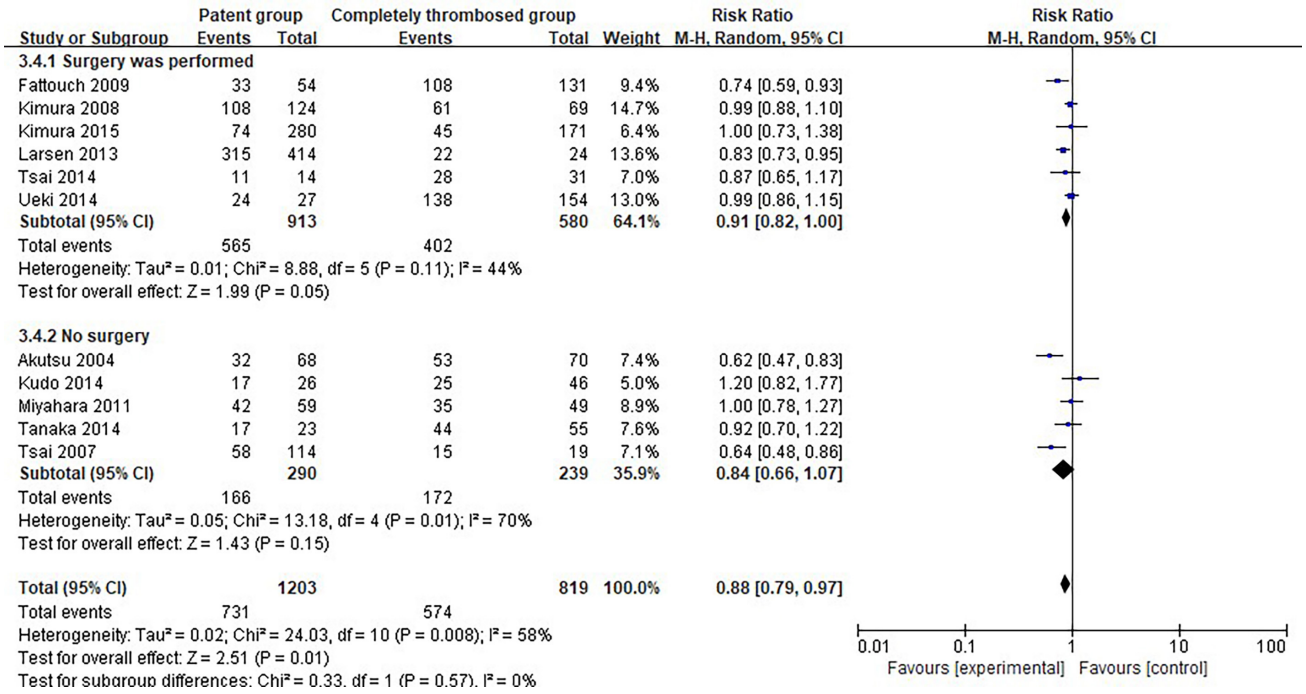

Fig. 8. Subgroup analysis of long-term survival of patients whether surgery or not.

computed tomography (CT) images. Due to different CT equipment and procedures, it may lead to heterogeneity of discord and control. In addition, although the measurement method is basically the difference between the first measured (d1) and the final postoperative (d2) aortic diameter divided by the time interval (T) between two CT images. However, studies still did not report measures, which is one source of potential heterogeneity. Although there is a large heterogeneity, the results cannot be completely considered unreliable, which still has some enlightenment for follow-up research. The heterogeneity of this result was significantly reduced when the Fattouch *et al*. [14] study was excluded. The source of heterogeneity in long-term survival may also be because this result is extracted from the Kaplan-Meier curve of a single study, and the difference in the calculation of the Kaplan-Meier curve in different studies may lead to the final heterogeneity.

At present, the specific mechanism of the false lumen state and the prognosis of AD patients is still unclear, but some scholars have put forward the following points of view. Some scholars believe that thrombus reduces pressure load on aneurysm wall and thus improves the hemodynamic situation in this area [28]. While others have reported that blood clots are not protective and do not reduce the risk of rupture. It was also suggested that thrombi release proteases, which may be associated with aneurysm enlargement and rupture. A study of thrombus-covered aneurysm walls suggests that the thrombus can be an obstacle to oxygen delivery, leading to hypoxia of the underlying wall, which may result in reduced thickness and strength, potentially leading to rupture [29–31]. Complete thrombosis of the false lumen is considered a prerequisite for post-dissection aortic healing, as flow and pressurization of the false lumen is thought to be responsible for late dilatation and rupture [24]. Therefore, patients with a completely thrombosed false lumen are expected to have improved survival during follow-up. A patent false lumen can be filled through the proximal entry tear and decompressed through the distal entry tear. In the most extreme cases, however, partial thrombus formation can occlude these distal tears, impeding outflow and creating dead ends. Increased pressure within the false lumen will lead to increased wall tension and increase the risk of aneurysm dilation, redissection, and rupture; therefore, increased mortality is expected in these patients [32,33]. At present, there are few studies in related fields, but our work will still inspire some clinical work. For example, in the treatment of AD patients, we can try not to preserve the patency of the false lumen so that patients can get a better prognosis. In addition, we can also minimize the occurrence of adverse events by providing different personalized medical care for patients with different false lumen types.

Personalized medicine can play a key role in preventing, monitoring and managing complications. For surgical trauma-related complications such as incision infection, wound dehiscence, etc. Personalized medicine can help predict the risk of wound healing in patients through genetic analysis and bacterial community research, and take corresponding preventive measures. For cardiovascular complications such as arrhythmia, myocardial infarction, etc. Based on the patient's electrocardiogram (ECG), blood biochemical indicators and clinical manifestations, personal-

ized medicine can help monitor cardiovascular conditions, detect and deal with problems early. For vascular complications such as aneurysm, arterial occlusion, etc. Based on genetic background and family history of arterial disease, personalized medicine can help identify high-risk patients and implement early interventions. For the recurrence or expansion of arterial dissection, personalized medicine can help monitor dissection, predict risk and develop intervention plan through regular imaging examination (such as CT scan) and genetic factor analysis. Personalized medicine can develop a customized treatment plan for each patient based on various factors such as the patient's genomic information, clinical data, and lifestyle. This approach can improve treatment outcomes, reduce the incidence of complications, and better meet patients' needs and risks. However, the implementation of personalized medicine requires comprehensive consideration of issues such as ethics, law, and privacy to ensure the rights and safety of patients.

Our research still has the following limitations: First, there are relatively few related fields, so our included literature is not very large, and the sample size is not large enough. Second, some uncontrollable confounding factors do not rule out possible bias. Third, some studies reported all-cause mortality instead of reporting deaths separately, so the results may have been overstated. Although the latest included literature is 2018, there are few studies on the false lumen of aortic dissection, and our study is currently the largest evidence-based medical study in related fields.

Conclusion

Patients with completely thrombosed aortic dissection have better outcomes in long-term survival, aortic event and smaller yearly aortic growth rate. And the risk of aortic rupture and hospital death in patients with patent false lumen is 7 times and nearly 3 times that of patients with completely thrombosed false lumen. Although there was no significant difference between Stanford A and Stanford B in terms of long-term survival, Stanford B had a smaller yearly aortic growth rate. Therefore, although the long-term survival and outcomes of patients with completely thrombosed are better, care should be taken in the short term, especially during hospitalization, to reduce the risk of in-hospital death and aortic rupture in patent patience.

Author Contributions

SZ and RL designed the trial. SZ, WS and SL were responsible for data analysis and writing of the manuscript. SL, BS and LX are responsible for the extraction of data and the production of pictures and tables. SL provides methodological support. RL read the full text and provided comments. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.5739.

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