

Predictive Value of D-dimer on Mortality in Patients with Acute Aortic Dissection

Shuangshuang Li

Changhai Hospital

Pengcheng Du

Changhai Hospital

Jian Dong

Changhai Hospital

Jian Zhou

Changhai Hospital

Zaiping Jing (✉ xueguanky@163.com)

Changhai Hospital <https://orcid.org/0000-0002-0434-4009>

Research article

Keywords: D-dimer, acute aortic dissection, in-hospital mortality, meta-analysis

Posted Date: December 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-114655/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Objective

To clarify the relation between D-dimer and in-hospital mortality of acute aortic dissection, a meta-analysis was performed by summarizing all relevant studies.

Methods

All related studies were retrieved and identified in PubMed and Embase databases. Precise data was extracted from standard articles, such as sample size, odds ratio, and 95% confidence interval. Then pooled odds ratio (OR) accompanying 95% confidence interval (CI) were calculated using random model. Study heterogeneity examined by Q test and I^2 statistic. Sensitivity analysis was performed to assess the stability of the results. Publication bias was assessed by Egger's test.

Results

Ten studies (1954 patients) that met the inclusion criteria were included in this review. The results suggested a link between D-dimer and in-hospital mortality of acute aortic dissection (OR=1.17 95%CI=1.08-1.27). With higher of cutoff value of D-dimer, the closer for the mortality of AAD, with ORs (95% CIs) ranging from 1.13(1.09–1.16) to 4.12 (1.56–10.93). The relationship was also found in six Type A AAD studies without heterogeneity (OR=1.13 95%CI=1.08-1.18). According to sensitivity analysis, the link was stable after exclusion of one study at a time. Publication bias was found among studies ($P=0.02$).

Conclusions

The result of this meta-analysis indicated that D-dimer maybe a predictor in-hospital mortality of acute aortic dissection patients. What's more, the higher of cutoff value of D-dimer, the stronger for the predictive ability.

Introduction

Acute aortic dissection (AAD) is a life-threatening disease requiring an early diagnosis and effective treatment to prevent from death. As estimated, the annual incidence of aortic dissection was about 3/100000 [1]. The in-hospital mortality rate of type A AAD and type B AAD were 24.4% and 10.7% [2], which remains a paramount concern for clinicians even after successful surgery. However, AAD inpatients always have unexpected adverse events, and transferred to a danger situation in several minutes, thus easily delaying the rescue opportunity. Given the atypical presentations, and time dependent mortality, sensitive and quicker predictive tools to identify patients at increased risk of death are paramount to take first-aid measures for clinicians.

Imaging equipment, such as computed tomography angiography (CTA), trans-esophageal echocardiography (TEE), or magnetic resonance angiography (MRA) is recognized as the powerful weapon for AAD diagnosis and treatment [3]. However, the use of these devices is based on typical symptoms, doctor's experience and high suspicious patients. As a result, high risk patients without atypical symptoms might be neglected. Besides, these imaging devices are invasive and expensive. The above severe condition indicated an insufficient medical supply in helping to identify patients in danger at an early time-point.

Biomarkers, such as D-dimer, CRP, cardiac troponin T and so on, were widely studied to predict in-hospital mortality of AAD [4, 5]. D-dimer, a degradation product of cross-linked fibrin, is reported highly elevated in AAD patients [6]. Its role as a "rule out" diagnosis biomarker has been widely studied in previous study [7]. The European Society of Cardiology guidelines introduced the use of d-dimer as a secondary filter in patients with suspect aortic dissection [8]. In recent years, it was proposed to use in prediction mortality of AAD patients [9]. However, heterogeneous results were shown for the relationship between D-dimer and in-hospital mortality of AAD. It should be noted that these studies both conducted with small sample size and conservative conclusions. We conducted this meta-analysis to summarize all the related articles to clarify the predict value of D-dimer for in-hospital mortality of AAD patients with a relatively large sample size.

Materials And Methods

This meta-analysis was performed in accordance with the standards set forth by the statement from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the guidelines for performing a Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [10–11].

Literature and search strategy

Combinations and derivatives of D-dimer, fibrin, fragment, acute aortic dissection were used as terms for retrieving in PubMed and Embase. In addition, the references of included articles were also retrieved. The literature search was limited to English language. If more than one article was published on the same cohort, only the recently published study was included. The literature search is updated till Dec.31, 2019.

Inclusion criteria and data extraction

Studies included in the system review met the following inclusion criteria: (1) evaluation of the predict value of D-dimer for in-hospital mortality of AAD patients; (2) written in English; (3) reporting ORs/RRs/HRs with 95% confidence intervals (CIs) or relevant data to calculate them. Case report, system review, conference abstracts and other researches were excluded based on the guidelines. Relevant data were extracted from the qualified articles using a standardized form. Two authors independently assessed the articles for compliance with the inclusion/exclusion criteria and entered the data in a predefined database. Discrepancy was resolved through discussion and repetitive analysis.

Statistical analysis

Random effects model was chosen to calculate pooled ORs/RRs with 95% CIs for D-dimer. Heterogeneity was assessed by the *Q*-test and the I^2 statistic. The significance for the *Q*-test was defined as $P < 0.10$. The I^2 statistic represents the amount of total variation attributed to heterogeneity. Low, moderate and high degrees of heterogeneity correspond to I^2 values of 25%, 50% and 75%, respectively. Sensitivity analysis after exclusion of each study at a time was performed to assess the stability of the results. Publication bias was assessed by funnel plot, and Egger's regression test was applied ($P < 0.05$ was considered statistically significant). Statistical analysis was conducted using STATA version 11 (Stata Corp LP, College Station, TX, USA).

Results

Search strategy of included studies

A search flowchart of relevant studies presented as Fig. 1. A total of 162 and 482 records were identified respectively in PubMed and Embase for potentially screening of title and abstracts. Remarkably, 248 articles were duplicated. 330 were excluded after screening of title and abstracts. 42 were not related to the topic after reading. 5 were systematic review. As a result, 19 studies were considered for inclusion. After reading, 4 were excluded due to Chinese writing, 1 for duplicated samples and 4 didn't provide relative data independently. Finally, 10 studies (1954 patients) that met the inclusion criteria were included in this review. A majority of the included patients were men. Six were from China. The D-dimer was measured once admission or within 48 h before any surgical procedure. Adjustment OR and 95%CI were extracted in the included studies. Detailed characteristics of included studies were displayed in Table 1-1 and 1-2.

Table 1-1

Characteristics of studies included in the meta-analysis of the association between D-dimer and in-hospital mortality of AAD

Study ^{year}	Study design	Country	Age	Male (%)	AAD cases	Type A AAD (%)	Mortality(%)	AAD diagnostic technique
Ohlmann,2006 ¹⁷	case-control	France	63.8±12.6	50.8	94	71.3	22(23)	TEE, CT, MRI ,angiography and autopsy
Weber,2006 ¹⁶	NA	Austria	62±16	55.6	27	100	13(48.1)	CT, echocardiography, or necropsy
Wen, 2013 ⁹	prospective study	China	48.9±7.6	84.2	114	56.1	31(27)	history, chest radiography, transthoracic or TEE, and CT.
Peng, 2013 ¹⁹	NA	China	58.4±13.1	74.6	280	50.4	91 (32.5)	CTA
Tian, 2014 ²⁰	prospective observation	China	52±11	72.2	133	100	19(14.3)	CT
Huang,2015 ²¹	prospective observation	China	48.5±11.5	75.9	212	100	27(12.7)	multidetector CT scanning
Fan,2015 ¹⁵	prospective observation	China	NA	75.3	570	100	42(8.1)	multidetector CT scanning
Li, 2016 ⁵	prospective cohort	China	56.5±13.8	68.3	103	100	36 (34.9)	TEE, TTE or CT.
Gorla, 2017 ¹⁴	prospective observation	Germany	64.6±13.6	69.2	159	56	31(19)	imaging, surgical or autopsy.
Itagaki,2018 ²²	retrospective	Japan	64.7±12.8	54.6	262	100	23 (8.8)	computed tomography (CT)

Note. The measurements are ordered by decreasing AUC.

Table 1-2

Characteristics of studies included in the meta-analysis of the association between D-dimer and in-hospital mortality of AAD

Study, year	Time of D-dimer test	D-Dimer cut-off value (ug/mL)	OR(95%CI)	Adjustment
Ohlmann,2006	a mean duration of symptoms of 1.2 ± 2.5days	>5.2	5.38(1.27–30.87)	female gender, presence of pericardial effusion, systolic arterial pressure 100 mm Hg, presence of shock
Weber,2006	NA	continuous	1.32(1.01–1.75)	age, diastolic blood pressure, treatment strategy, ECG evidence of left ventricular hypertrophy (Sokolow or Cornell index), and anatomical extent of disease
Wen, 2013	within 48 h after admission	≥ 5.67	3.272(1.638–6.535)	the type of AD, history of smoking, admission systolic blood pressure, admission diastolic blood pressure, aortic diameter, onset of symptoms to hospital admission and CRP
Peng, 2013	on admission	≥ 5.0	2.21(0.16–5.4)	NA
Tian, 2014	on admission	continuous	1.086(0.109–1.157)	adjustment for age, systolic blood pressure, platelet counts, and intervals from symptom onset to hospital
Huang,2015	on admission	continuous	1.12(1.07–1.18)	adjustment for age, gender, admission WBC counts, surgical treatment
Fan,2015	on admission	continuous	1.15(1.11–1.21)	age,gender and other inflammatory factors
Li, 2016	on admission	continuous	1.124(0.928–1.535)	Admission systolic blood pressure, surgical or interventional treatment, maximal aortic diameter, Maximal aortic diameter, high-sensitivity C-reactive protein, platelet count
Gorla, 2017	on admission	≥ 9	3.26(1.12–9.46)	surgery/thoracic endovascular aortic repair (TEVAR)
Itagaki,2018	on admission	> 8.3	11.83(1.21–115.53)	Morphologic class, extent of dissection, and false lumen status, and differences between patient groups
NA represent there is not relative data in studies.				

Meta-analysis Results

The results suggested that D-dimer was associated with AAD mortality (OR = 1.17 95%CI = 1.08–1.27) (Fig. 2). According to the value of D-dimer, the included studies were divided into three groups. Group one included three studies with a D-dimer cutoff > 5.0 ug/mL. The forest map suggested a link between D-dimer and in-hospital mortality of AAD (OR = 2.92 95%CI = 1.79–4.77), no heterogeneity between studies ($I^2 = 0.0\%$, $P = 0.557$). In Group two, the relationship remained for five studies with continuous D-dimer value (OR = 1.13 95%CI = 1.10–1.16). Group three included two studies with D-dimer > 8.0 ug/mL, and the pooled OR also indicated a predictive value of D-dimer to AAD mortality (OR = 4.12 95%CI = 1.56–10.93). The association remained for six studies which explored the relation between D-dimer and mortality of Type A AAD patients (OR = 1.13 95%CI = 1.08–1.18) (Fig. 3).

Sensitivity analysis and Potential Publication bias

The results were stable after sensitivity analysis, with ORs (95% CIs) ranging from 1.13(1.09–1.16) to 1.14 (1.10–1.18) (Fig. 4). Publication bias was found among studies ($P = 0.02$, Fig. 5).

Discussion

To our knowledge, this is the first meta-analysis to explore the relationship between D-dimer and in-hospital mortality of acute aortic dissection. After pooling the relevant studies, a link between D-dimer and in-hospital mortality was found. Much more than this, the predicted value was more significant with higher D-dimer. It may be an effective predictive biomarker for clinicians to identify patients at high risk of death.

As we know, the role of D-dimer used as an initial diagnosis marker was widely studied^[11–13]. However, the evidence of predicting role of D-dimer for AAD in-hospital mortality is not only scarce but controversial^[14–15]. In 2006, Weber et al. found that absolute D-dimer concentrations can forecast in-hospital mortality of type A AAD patients independently [OR and 95%CI: 1.32(1.01–1.75)]^[16]. A similar relationship was observed in the study conducted by Ohlmann et al. They found that D-dimer may reach a high level of above 20ug/mL in some AAD patients three hours after the symptoms onset, and the concentration was high in dead than survival patients^[17]. In the present meta-analysis, we combined all the eligible studies together and confirmed the link between D-dimer and in-hospital mortality of AAD. What's more, we found a stronger predictive power with higher D-dimer cutoff value.

The mechanism that D-dimer can predicted mortality of AAD remains unclear. According to previous researches, dissection anatomical extent was assumed to associate with the amount of coagulation and fibrinolytic activation. Tissue factor of dissected aorta triggered coagulation cascade, the activation of extrinsic pathway can be counteracted by endogenous fibrinolytic activity. While, the serum D-dimer, as the degradation product of cross-linked fibrin, may rise due to endogenous fibrinolytic activity^[18]. An increased plasma D-dimer may be a manifestation of severe anatomical degree of dissection and greater mortality. D-dimer might be high when ascending aorta is involved for reflecting the higher frequency of unfavorable outcomes. According to our study, the association was obvious and stable in type A AAD. It is better to separate the type of AAD when using D-dimer to predict the in-hospital mortality of AAD patients.

This meta-analysis had several strengths. Firstly, we included both case-control and prospective studies to clarify the relationship between D-dimer and in-hospital mortality of AAD. Secondly, a large number of participants and cases guaranteed the sufficient statistical power to draw the credible conclusions. Third, in the current meta-analysis, the covariate adjusted OR and 95% CI were extracted from each study, which increased the accuracy of the summary estimation. However, several limitations should also be considered. Firstly, the included studies were mainly conducted in China. Therefore, the finding might be limited to apply to other countries. Secondly, the included studies adjusted for different confounders might have influenced our results. Lastly, publication bias was found among studies.

Conclusions

The result of this meta-analysis indicated that D-dimer maybe a predictor in-hospital mortality of acute aortic dissection patients. What's more, the higher of cutoff value of D-dimer, the stronger for the predictive ability.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of the Changhai Hospital, Naval Military Medical University.

Consent for publication

The authors thank the patients for informed consent to publication of data.

Availability of data and materials

All the data and materials can be available.

Competing interest

None declared.

Authors' contributions

Shuangshuang Li: Data collection; Formal analysis; Writing original draft. Pengcheng Du: Data curation; Formal analysis; Investigation. Jian Dong: Formal analysis; Resources. Jian Zhou and Zaiping Jing: Conceptualization; Funding acquisition; Project administration & Supervision.

Funding

This work is supported by Shanghai Science and Technology Innovation Program (17411954100 to Zaiping Jing) and by Changhai hospital Youth Start-up Fund (CH201804 to Shuangshuang Li).

Acknowledgements

No relationship with industry.

References

1. Meszaros I, Morocz J, Szilvi J, Schmidt J, Tornoci L, Nagy L and Szepl L. Epidemiology and clinicopathology of aortic dissection. *Chest*. 2000;117:1271-8.
2. Pape LA, Awais M, Woznicki EM, Suzuki T, Trimarchi S, Evangelista A, Myrmet T, Larsen M, Harris KM, Greason K, Di Eusanio M, Bossone E, Montgomery DG, Eagle KA, Nienaber CA, Isselbacher EM and O'Gara P. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. *J Am Coll Cardiol*. 2015;66:350-8.
3. Baliga RR, Nienaber CA, Bossone E, Oh JK, Isselbacher EM, Sechtem U, Fattori R, Raman SV and Eagle KA. The role of imaging in aortic dissection and related syndromes. *JACC Cardiovasc Imaging*. 2014;7:406-24.
4. Mori K, Tamune H, Tanaka H and Nakamura M. Admission Values of D-dimer and C-reactive Protein (CRP) Predict the Long-term Outcomes in Acute Aortic Dissection. *Intern Med*. 2016;55:1837-43.
5. Li G, Wu XW, Lu WH, Cheng J, Wu XY, Ai R, Zhou ZH, Tang ZZ and Liao YH. High-sensitivity cardiac troponin T: A biomarker for the early risk stratification of type-A acute aortic dissection? *Arch Cardiovasc Dis*. 2016;109:163-70.
6. Eggebrecht H, Naber CK, Bruch C, Kroger K, von Birgelen C, Schmermund A, Wichert M, Bartel T, Mann K and Erbel R. Value of plasma fibrin D-dimers for detection of acute aortic dissection. *J Am Coll Cardiol*. 2004;44:804-9.
7. Asha SE and Miers JW. A Systematic Review and Meta-analysis of D-dimer as a Rule-out Test for Suspected Acute Aortic Dissection. *Ann Emerg Med*. 2015;66:368-78.
8. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, Evangelista A, Falk V, Frank H, Gaemperli O, Grabenwoger M, Haverich A, Jung B, Manolis AJ, Meijboom F, Nienaber CA, Roffi M, Rousseau H, Sechtem U, Sirnes PA, Allmen RS, Vrints CJ; ESC Committee for Practice Guidelines. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2873–2926. doi: 10.1093/eurheartj/ehu281.
9. Wen D, Du X, Dong JZ, Zhou XL and Ma CS. Value of D-dimer and C reactive protein in predicting in-hospital death in acute aortic dissection. *Heart*. 2013;99:1192-7.

10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009; 62(10): e1-34.
11. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283(15): 2008-12.
12. Dong J, Duan X, Feng R, Zhao Z, Feng X, Lu Q, Jing Q, Zhou J, Bao J and Jing Z. Diagnostic implication of fibrin degradation products and D-dimer in aortic dissection. *Sci Rep.* 2017;7:43957.
13. Suzuki T, Distant A, et al. Diagnosis of acute aortic dissection by D-dimer the international Registry of acute aortic dissection substudy on biomarkers (IRAD-Bio) experience[J]. *circulation*, 2009, 119(20): 2702.
14. Nazerian P, Mueller C, Soeiro A M, et al. Diagnostic accuracy of the aortic dissection detection risk score plus D-dimer for acute aortic syndromes: the ADVISED Prospective Multicenter Study[J]. *Circulation*, 2018, 137(3): 250-258.
15. Gorla R, Erbel R, Kahlert P, Tsagakis K, Jakob H, Mahabadi AA, Schlosser T, Eggebrecht H, Bossone E and Janosi RA. Diagnostic role and prognostic implications of D-dimer in different classes of acute aortic syndromes. *Eur Heart J Acute Cardiovasc Care.* 2017;6:379-388.
16. Fan X, Huang B, Lu H, Zhao Z, Lu Z, Yang Y, Zhang S and Hui R. Impact of Admission White Blood Cell Count on Short- and Long-term Mortality in Patients With Type A Acute Aortic Dissection: An Observational Study. *Medicine (Baltimore).* 2015;94:e1761.
17. Weber T, Rammer M, Auer J, Maurer E, Aspöck G and Eber B. Plasma concentrations of D-dimer predict mortality in acute type A aortic dissection. *Heart.* 2006;92:836-7.
18. Ohlmann P, Faure A, Morel O, Petit H, Kabbaj H, Meyer N, Cheneau E, Jesel L, Epailly E, Desprez D, Grunebaum L, Schneider F, Roul G, Mazzucotteli JP, Eisenmann B and Bareiss P. Diagnostic and prognostic value of circulating D-Dimers in patients with acute aortic dissection. *Crit Care Med.* 2006;34:1358-64.
19. Weber T, Auer J, Eber B, Nienaber CA and Eagle KA. Value of d-dimer testing in acute aortic dissection. *Circulation.* 2004;109:E24.
20. Peng W, Zhu QY, Zhou XH and Chai XP. A Simple Emergency Prediction Tool for Acute Aortic Dissection. *Iran J Public Health.* 2013;42:1085-91.
21. Tian L, Fan X, Zhu J, Liang Y, Li J and Yang Y. Plasma D-dimer and in-hospital mortality in patients with Stanford type A acute aortic dissection. *Blood Coagul Fibrinolysis.* 2014;25:161-6.
22. Huang B, Yang Y, Lu H, Zhao Z, Zhang S, Hui R and Fan X. Impact of d-Dimer Levels on Admission on Inhospital and Long-Term Outcome in Patients With Type A Acute Aortic Dissection. *Am J Cardiol.* 2015;115:1595-600.
23. Itagaki R, Kimura N, Mieno M, et al. Characteristics and Treatment Outcomes of Acute Type A Aortic Dissection With Elevated D-Dimer Concentration. *Journal of the American Heart Association*, 2018, 7(14): e009144.

Figures

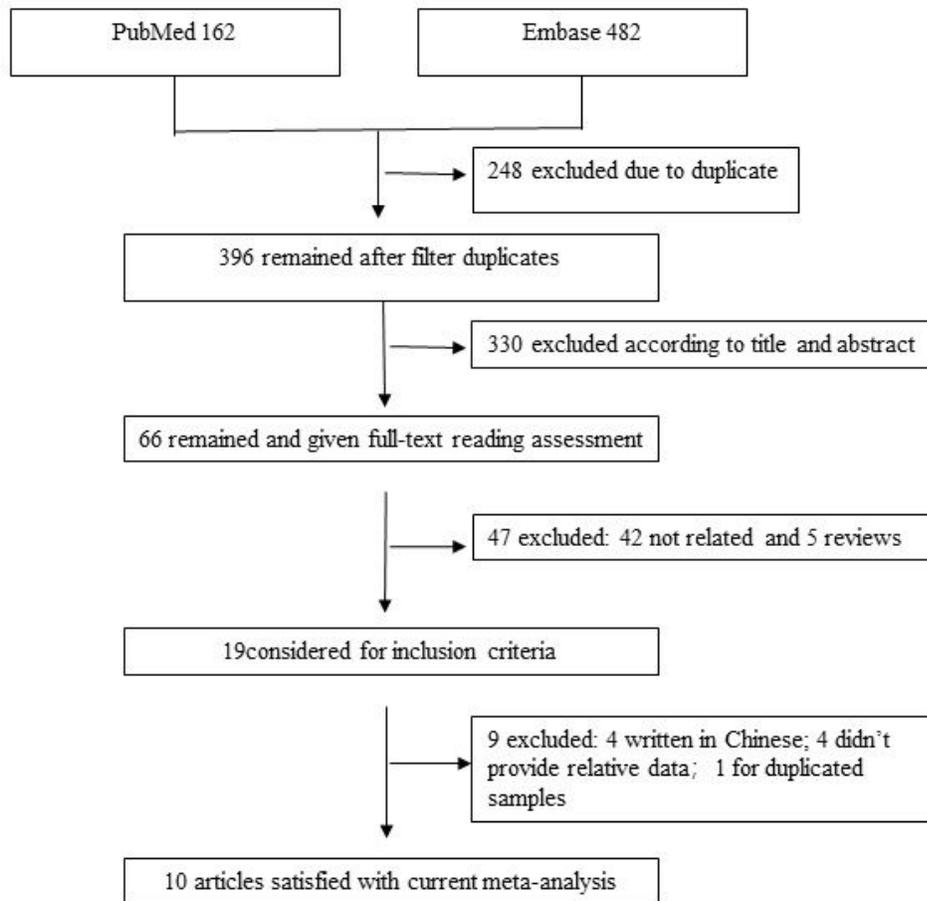


Figure 1

Flow chart of article selection

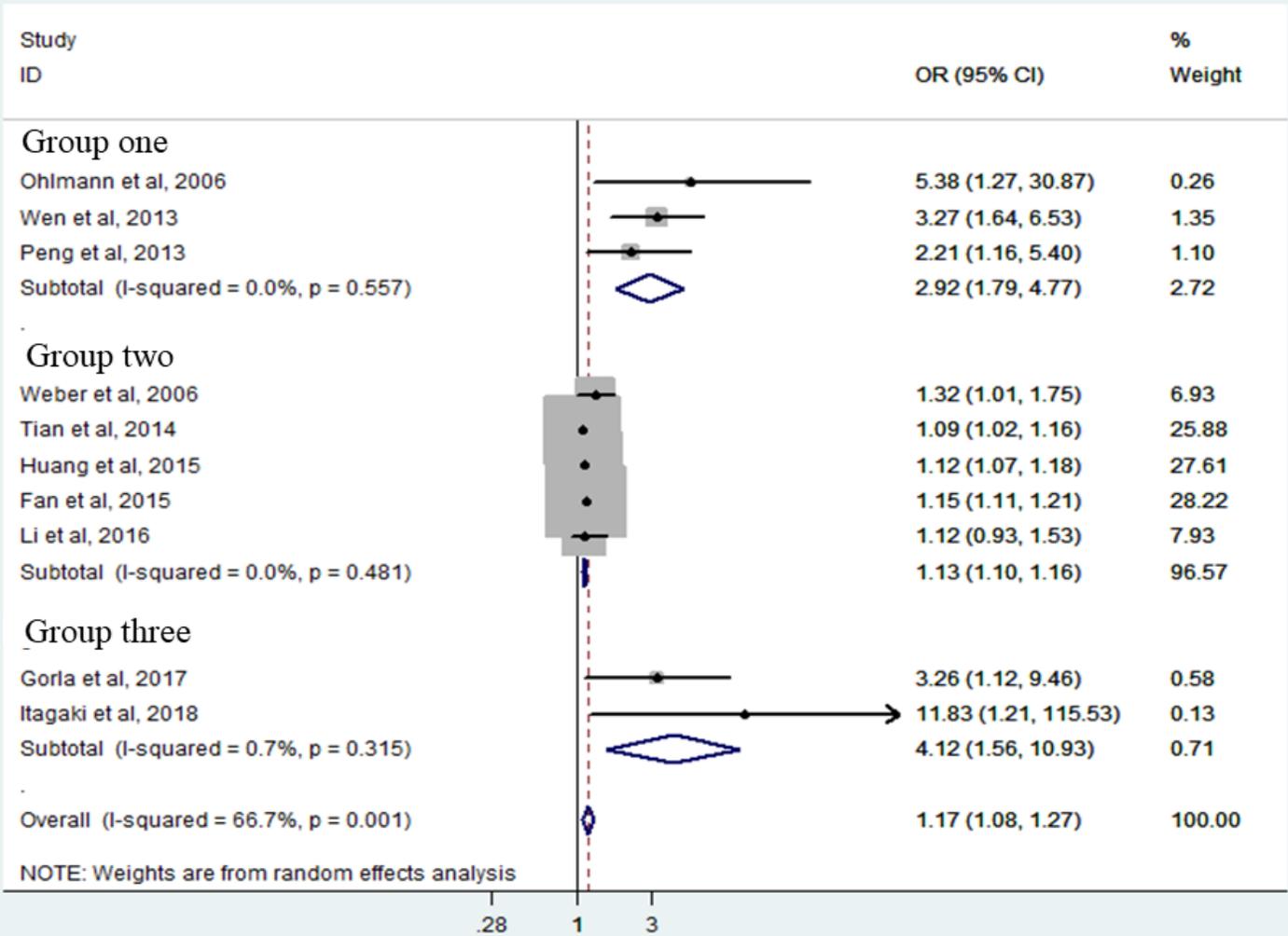


Figure 2

Forest plot of the association between D-dimer and AAD

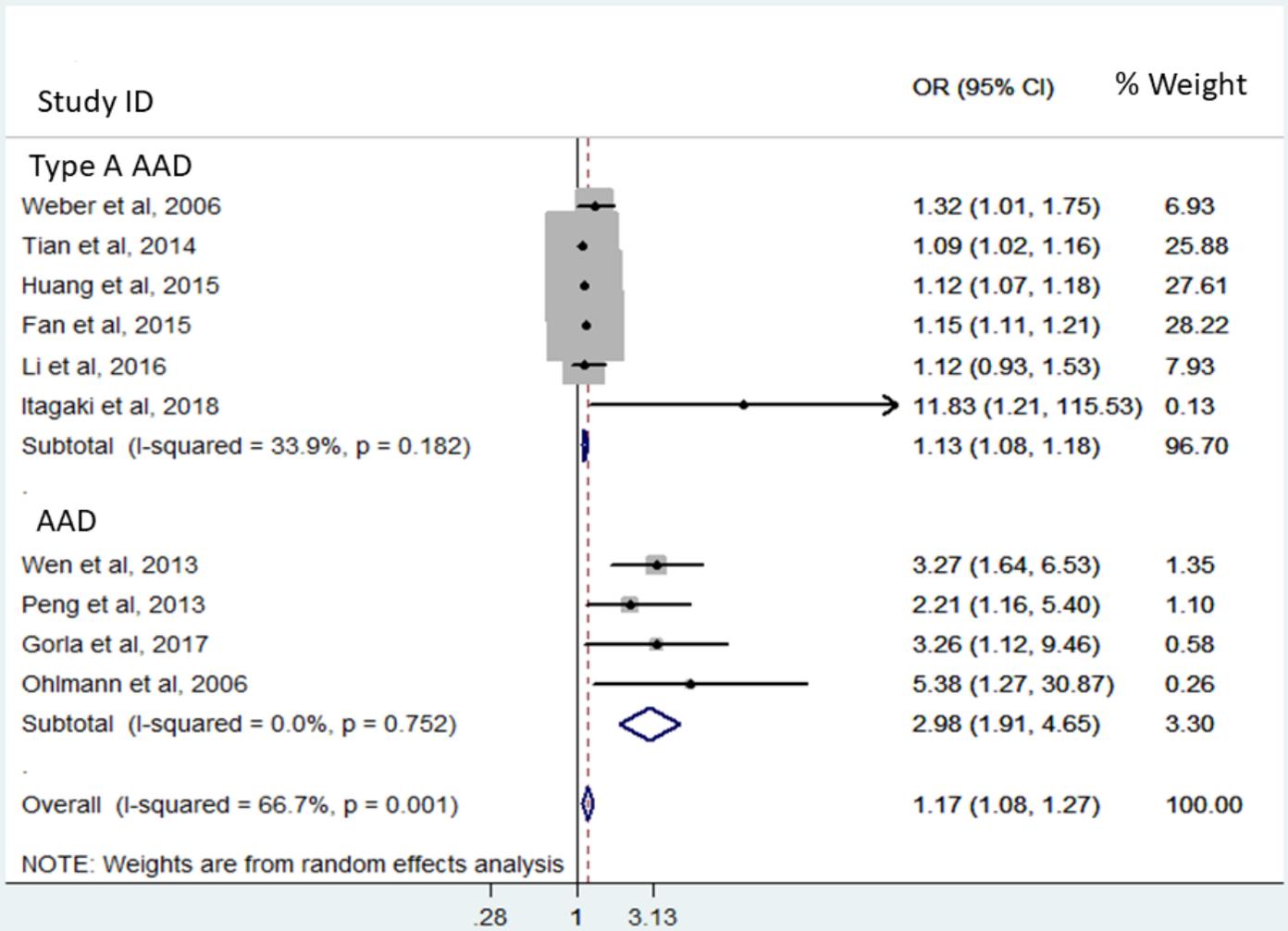


Figure 3

Subgroup analysis of the association between D-dimer and AAD by aortic type

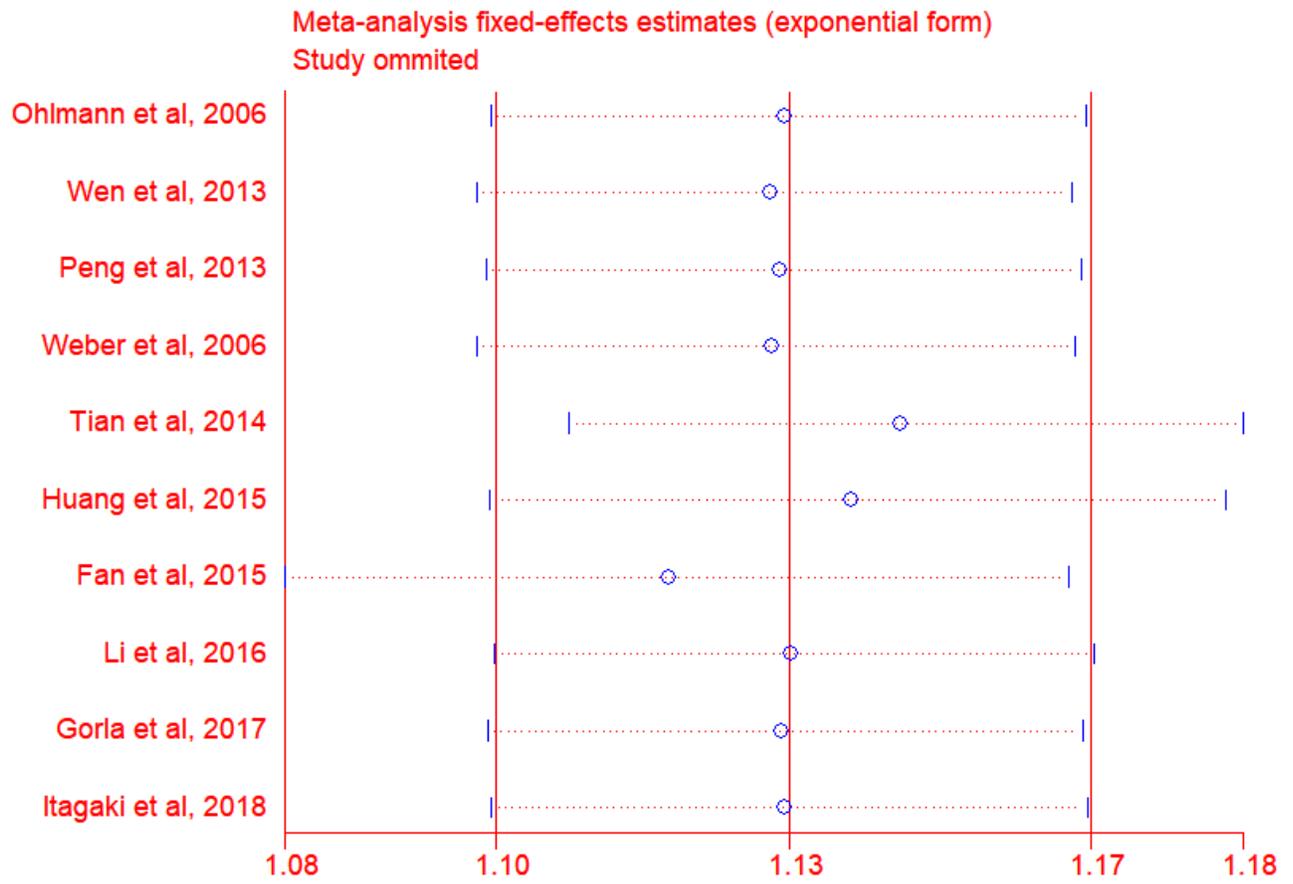


Figure 4

Result of sensitivity analysis

Begg's funnel plot with pseudo 95% confidence limits

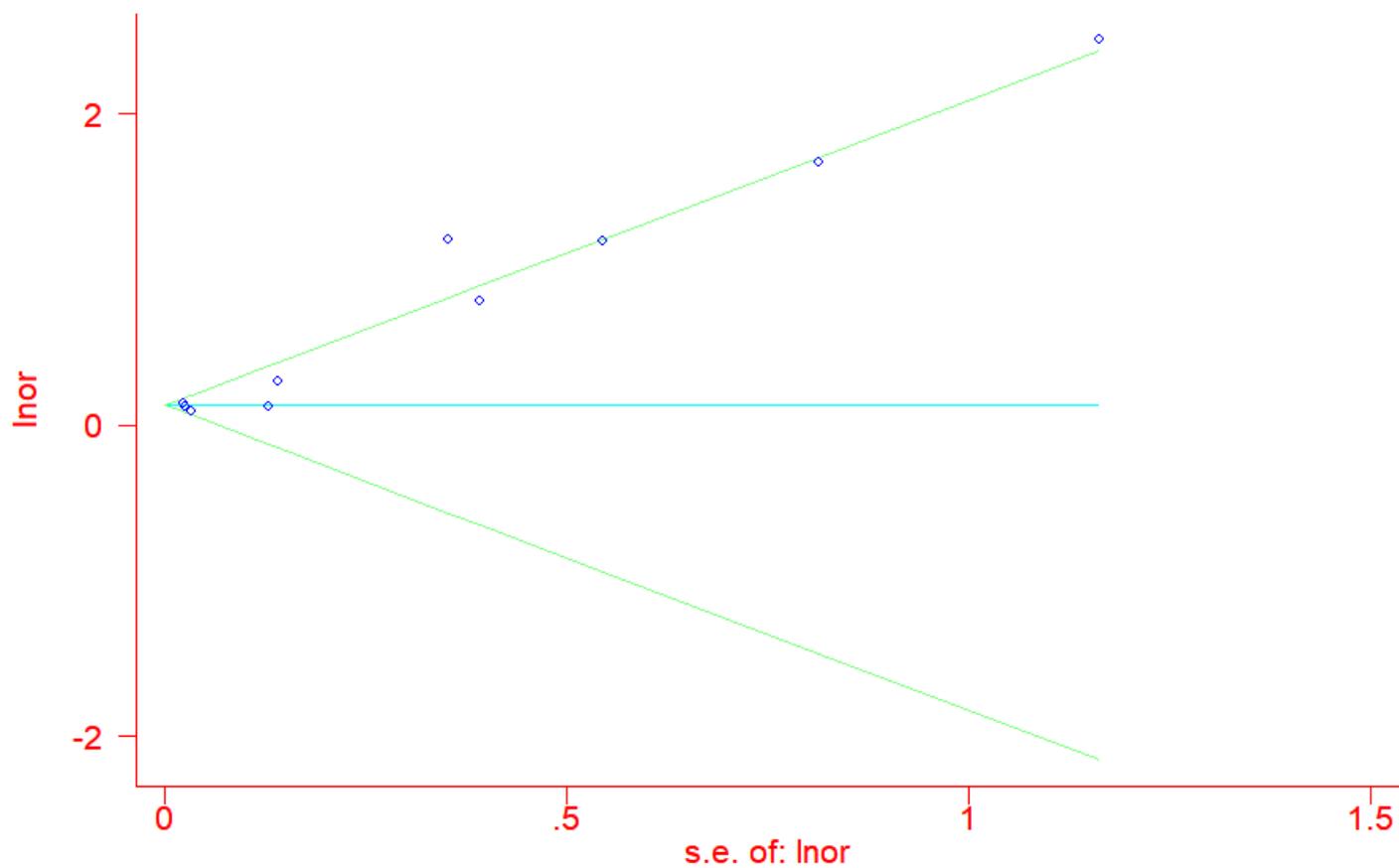


Figure 5

Funnel plot about the publication bias of included studies