

# Risk Factors for Postoperative Permanent Neurological Dysfunction After Stanford Type A Aortic Dissection: A Systematic Review and Meta-Analysis of 11382 Cases

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## ABSTRACT

**Objective:** To systematically evaluate the risk factors for permanent neurological dysfunction (PND) after Stanford type A aortic dissection (TAAD).

**Method:** Electronic databases included PubMed, Embase, Web of Science, CNKI, WanFang Data, VIP, and CBM. We collected studies about risk factors for PND after TAAD was published from inception to December 2021. Two authors independently assessed the quality of the studies, and a meta-analysis was performed by RevMan 5.3 Software.

**Results:** A total of 20 studies involved 11382 cases, and among them, 1321 patients suffered PND, including 34 predictive risk factors. The meta-analysis showed that age (OR=1.11, 95% CI (1.06, 1.16),  $P < 0.0001$ ), preoperative PND (OR=2.95, 95% CI (2.14, 4.07),  $P < 0.00001$ ), retrograde tear in the ascending aorta (OR=6.67, 95% CI (3.23, 13.79),  $P < 0.00001$ ) were independent risk factors for PND after TAAD surgery.

**Conclusions:** Current evidence shows that age, preoperative PND, retrograde tearing in the ascending aorta are risk factors for PND after TAAD. These factors can be used to identify high-risk patients, providing guidance for medical staff to develop perioperative preventive strategies to reduce the incidence of PND. The results should be validated by higher-quality studies.

## INTRODUCTION

Stanford type A aortic dissection (TAAD) is a life-threatening condition associated with high morbidity and mortality rates; emergency surgery is usually required. Neurological dysfunction is a serious postoperative complication of TAAD, that includes transient neurological dysfunction (TND) and permanent neurological dysfunction (PND). PND refers to new postoperative cerebral infarction,

cerebral hemorrhage, ischemic-hypoxic encephalopathy, or paraplegia with positive cranial computed tomography or magnetic resonance imaging results that cannot be resolved during hospitalization. Related studies in the United States, Germany, and China reported an incidence of postoperative PND of 4.8%–13.4% [Krüger 2011; Wang 2020; Ghoreishi 2020]. The risk of acute kidney injury, respiratory failure, death, and prolonged hospitalization are increased, and long-term survival and patient quality of life are reduced in patients with postoperative PND [Krüger 2011; Ghoreishi 2020; Dumfarth 2018; Minakawa 2010]. Therefore, it is important to actively prevent and treat PND after TAAD to prevent and reduce its postoperative occurrence. In the last 10 years, several studies have reported that factors such as preoperative brain injury, poor preoperative perfusion, arterial cannulation location, cerebral protection strategies when circulation is stopped, and temperature management during extracorporeal circulation are closely related to postoperative PND [Ghoreishi 2020; Guo 2015; Preventza 2020]. To effectively identify patients with postoperative PND as early as possible, many scholars have reported risk factors associated with postoperative PND, but the inclusion of factors was inconsistent among studies and the results were variable. Therefore, this study systematically evaluated the literature for risk factors for PND in TAAD and performed a meta-analysis to explore these risk factors and guide clinical staff to identify the high-risk group to enable early intervention for PND and improve patient prognosis.

## MATERIALS AND METHODS

### *Inclusion and exclusion criteria:*

#### **Inclusion criteria**

- (1) Study type: prospective cohort and case-control.
- (2) Study population: age  $\geq 18$  years; having undergone Stanford type A aortic dissection surgery using any surgical modality.
- (3) Exposure factors: exposure factors reported in two or more studies with the same definition; preoperative transient nerve injury defined as a preoperative transient ischemic attack, syncope, etc. and the absence of focal lesions on CT and MRI.
- (4) Outcome: PND, defined as the occurrence of postoperative cerebral ischemia, cerebral hemorrhage,

Received February 14, 2022; accepted March 24, 2022.

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ischemic-hypoxic encephalopathy, or paraplegia; confirmed use of cranial CT or MRI of the head; no symptom resolution after treatment during hospitalization.

#### Exclusion criteria

- (1) Repeat publication or translated papers and case studies.
- (2) Literature for which data are incomplete and cannot be extracted.
- (3) Non-Chinese or non-English papers.
- (4) Univariate analysis of postoperative PND occurrence only with no multivariate analysis results.

**Literature search strategy:** The PubMed, EMBase, Web of Science, CNKI, WanFang Data, VIP, and CBM databases were searched for relevant articles published from database conception through December 2021. The Chinese and English search terms included subject terms and free words, such as aortic dissection, neurological injury, brain complications, neurological complications, cerebral infarction, stroke, cerebrovascular accident, stroke, cerebral hemorrhage, ischemic-hypoxic encephalopathy, paraplegia, risk factors, predictors, influential factors, correlates, predictors, and correlation. The reference lists of the included papers were manually searched to identify any other relevant studies. The strategy used to search PubMed as an example is shown in Supplementary 1. (Supplementary Table 1)

**Literature screening, data extraction, and quality evaluation:** Two researchers independently screened the literature, retrieved the studies, and extracted the relevant information. In cases of disagreement, the two researchers reached a consensus by discussion or consultation with a third researcher. The authors were contacted in cases of incomplete information. After two researchers independently screened the titles and abstracts in the initial screening, the full text was further read to identify studies for inclusion based on the inclusion and exclusion criteria. The data extraction included: (1) basic study characteristics including title, authors, and year of publication; (2) basic study population characteristics including age, sex, the total number of patients in the PND and non-PND groups, TAAD diagnostic criteria, and PND diagnostic criteria; (3) key elements of the literature quality evaluation; and (4) outcome-related markers, including the incidence of PND, independent risk factors for PND after TAAD.

The two investigators used the Newcastle–Ottawa Quality Scale to separately evaluate the quality of studies, including study subject selection, intergroup comparability, and exposure factors. The NOS scale includes three domains and eight items, of which 9 points is the full mark, and studies with 5–9 points are considered of high quality.

**Statistical analysis:** The statistical analyses were performed by RevMan 5.3 software. The odds ratios (ORs) and 95% confidence intervals (CIs) of the independent risk factors for PND after TAAD were extracted, and the results were combined with two and more risk factors, using the inverse variance method for ORs and 95% CIs were obtained.

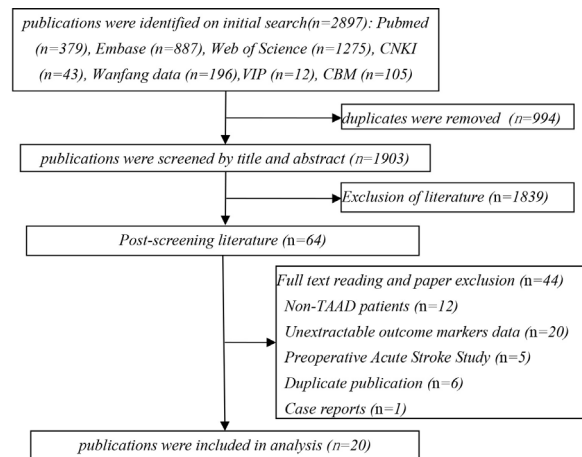


Figure 1. Flow chart showing selection and screening process.

Descriptive analyses were performed for data that could not be combined or one risk factor. The heterogeneity of the included studies was tested using the Q test and  $I^2$  test; if  $P > 0.1$  and  $I^2 \leq 50\%$ , the included studies were considered homogenous, and the fixed effects model was selected. If  $P \leq 0.10$  and  $I^2 > 50\%$ , the included studies were considered heterogeneous, and the random-effects model was used for data merging. Finally, a sensitivity analysis was used to explore the stability of the results, and a funnel plot was used to analyze publication bias.

## RESULTS

**Literature search and screening results:** A total of 2897 papers on risk factors for PND after TAAD were identified using the search strategy. Of them, 64 were subjected to full-text screening. Finally, 20 were included in this meta-analysis. (Figure 1)

**Basic characteristics of the included studies and risk of bias evaluation:** After the literature screening, 20 papers ultimately were included, of which one was a prospective study, and the rest were retrospective case-control studies. There was a total of 11382 patients and 1321 postoperative PND patients. The incidence of postoperative PND after TAAD was 3.34%–21.57%, and a total of 34 independent risk factors were included. The NOS risk of bias assessment was used, with a score of 6–9 points. Six studies had a perfect score, and the overall study quality was high. (Table 1)

**Preoperative factors:** The preoperative factors involved in the included studies were age [Yu 2019; Lu 2017; Lang 2020; Liu 2016; Liu 2014; Zhao 2018], preoperative PND [Xue 2021; Lu 2017; Zhao 2021; Liu 2016; Liu 2014; Zhao 2018], and retrograde tears in the ascending aorta [Zhao 2018; Zhao 2020; Zhao 2021]. Age, preoperative PND, and retrograde tears in the ascending aorta were homogeneous among the studies and analysed using a fixed-effects model. Meta-analysis results showed that age (OR, 1.11; 95% CI, 1.06–1.16;  $P < 0.0001$ ), preoperative PND (OR, 2.95; 95% CI, 2.14–4.07;  $P < 0.00001$ ), and retrograde tear in the

Table 1. Study characteristics (n/%/ )

First author	Year	Country	Study type	Study	N	PND definition	M/F	PND	Prevalence	Mean age	Risk factor	NOS
Cho	2020	Japan	Case-control	2012-2019	202	Stroke	114/88	25/177	12.37	68	1	7
Dumfarth	2020	Australia	Case-control	2000-2007	320	Brain hemorrhage, ischemia	NR	60/260	18.75	59.3±13.7	2, 3	8
Ghoreishi	2020	USA	Case-control	2014-2017	7353	Stroke	4846/2507	945/6408	12.85	60	3, 4, 5, 6, 7, 8, 9, 10	9
Xue	2021	China	Case-control	2010-2017	746	Brain hemorrhage, stroke	566/180	35/711	4.69	52.1±13.0	11, 12, 13, 14, 15, 16	8
Zhang	2020	China	Prospective cohort	2016-2017	76	Stroke	61/15	10/66	13.16	45.8±9.9	17	9
Haldenwang	2012	Germany	Case-control	2003-2010	122	Stroke	85/37	20/102	16.39	58.6±12.5	18, 19	7
Yu	2019	China	Case-control	2013-2015	98	coma, sensory or motor impairment	NR	13/85	13.27	50.41±11.38	20, 21, 22	8
Dumfarth	2018	Australia	Case-control	2000-2017	303	Stroke	218/85	48/255	15.84	58.9±13.6	2, 23, 24, 25	9
Zhao	2018	China	Case-control	2013-2016	255	Stroke or coma	201/54	18/237	7.1	41±16	26, 27	8
Jiang	2018	China	Case-control	2013-2017	85	Stroke, coma, hemiplegia and paraplegia	62/23	10/75	11.76	47.6±11.7	4	9
Lu	2017	China	Case-control	2010-2017	82	Stroke	62/20	3/79	3.66	42.0±8.6	11, 20	9
Zhao	2020	China	Case-control	2015-2019	132	Stroke	107/25	19/113	14.39	46.7±11.7	26, 27, 28, 29	8
Wang	2020	China	Case-control	2015-2019	85	Stroke	71/14	8/77	9.41	47.95±10.62	5, 10	7
Zhao	2021	China	Case-control	2015-2018	174	Stoke	137/37	32/142	18.39	47.8±10.1	11, 26, 27, 30	7
Lang	2020	China	Case-control	2018-2019	51	Brain hemorrhage, stroke	37/14	11/40	21.57	55.1±12.3	20	6
Li	2020	China	Case-control	2012-2019	116	Stroke	72/44	15/101	12.93	44.3	31, 32	7
Xu	2020	China	Case-control	2013-2019	245	Coma, sensory or motor impairment	155/90	16/229	6.53	52.36±11.07	10, 18, 33, 34	9
Liu	2016	China	Case-control	2006-2012	388	Stroke	303/85	13/375	3.35	45.9±12.8	11, 20	7
Liu	2014	China	Case-control	2005-2011	329	Stroke	260/69	11/318	3.34	45±10.4	11, 20	7
Zhao	2018	China	Case-control	2010-2015	220	Brain hemorrhage, stroke	153/67	9/211	4.09	68.72±5.63	11, 20	7

N, number of patients included in the study; M/F, male/female; PND, permanent neurological dysfunction. Risk factors: 1, brachiocephalic artery dissection; 2, preoperative CPR; 3, preoperative transient nerve injury; 4, hypertension; 5, axillary artery cannulation; 6, aortic cannulation; 7, innominate artery cannulation; 8, total arch replacement; 9, retrograde perfusion; 10, extracorporeal circulation duration; 11, preoperative PND; 12, preoperative limb ischemia; 13, end-stage renal disease; 14, salvage surgery; 15, low-flow cerebral perfusion; 16, preoperative paraplegia; 17, carotid intima-media thickness; 18, preoperative EUROSCORE score; 19, aortic occlusion duration; 20, age; 21, preoperative platelet count; 22, prolonged intraoperative hemostasis duration; 23, bovine aortic arch; 24, preoperative malperfusion; 25, impaired perfusion in the right carotid artery; 26, retrograde tear in the ascending aorta; 27, aortic arch tear; 28, length of surgery; 29, hypotension; 30, common carotid artery dissection; 31, circulatory arrest duration; 32, postoperative low cardiac output; 33, total leukocyte count; 34, D-dimer

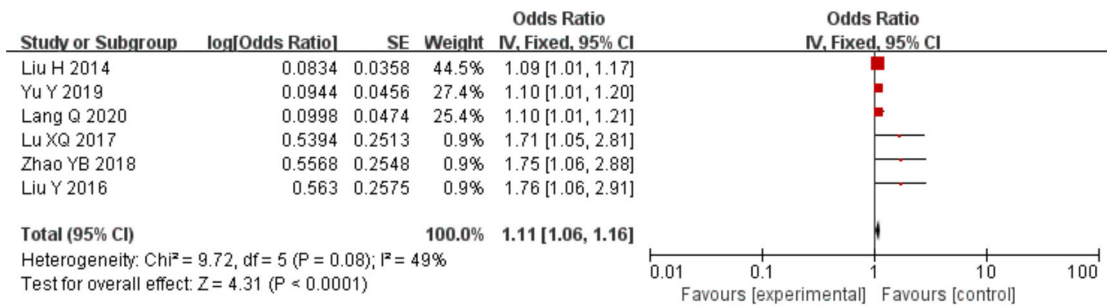


Figure 2. Forest plot showing the relationship between age and postoperative PND

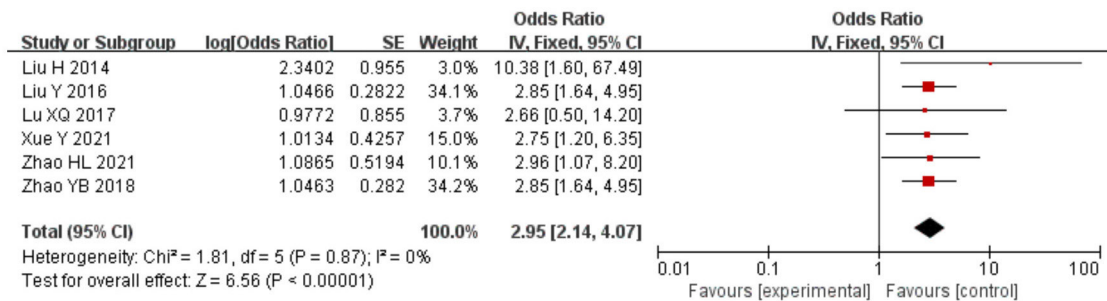


Figure 3. Forest plot showing the relationship between preoperative PND and postoperative PND

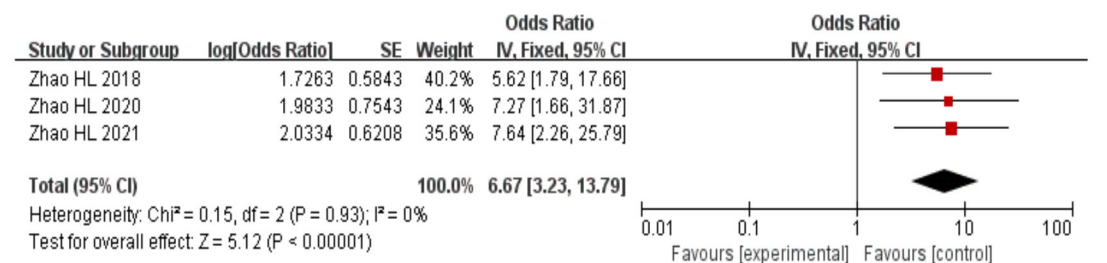


Figure 4. Forest plot showing the relationship between retrograde tears in the ascending aorta and postoperative PND

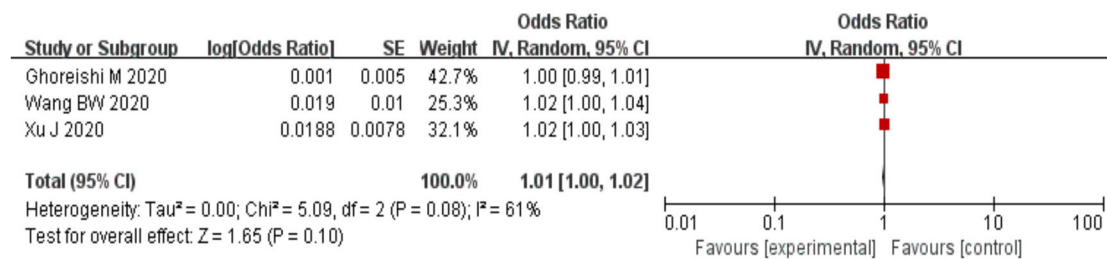


Figure 5. Forest plot showing the relationship between extracorporeal circulation time and postoperative PND

ascending aorta (OR, 6.67; 95% CI, 3.23–13.79; P = 0.00001); were risk factors for PND after TAAD. (Figure 2) (Figure 3) (Figure 4) The other preoperative risk factors are shown in Table 2. (Table 2)

**Intraoperative factors:** The intraoperative factor involved in the included studies was extracorporeal circulation

duration [Ghoreishi 2020; Wang 2020; Xu 2020], which was heterogeneous between studies and analyzed using a random-effects model, and the results of the meta-analysis showed that extracorporeal circulation duration (OR, 1.01; 95% CI, 1.00–1.02; P = 0.10) was not risk factor for PND after TAAD. (Figure 5) The other intraoperative risk factors are shown in

Table 2. Results of risk factors

Risk factor	Included studies	OR (95% CI)
Preoperative age	6 [Yu 2019; Lu 2017; Lang 2020; Liu 2016; Liu 2014; Zhao 2018]	OR=1.11(1.06-1.16)
Preoperative PND	6 [Xue 2021; Lu 2017; Zhao 2021; Liu 2016; Liu 2014; Zhao 2018]	OR=2.95(2.14-4.07)
Preoperative transient nerve injury	2 [Ghoreishi 2020; Dumfarth 2020]	OR =1.92(1.06-3.48)
Preoperative CPR	2 [Dumfarth 2018; Dumfarth 2020]	OR=6.62(2.40-18.31)
Preoperative paraplegia	1 [Xue 2021]	OR=24.707(1.987-307.16)
Brachiocephalic artery dissection	1 [Cho 2021]	OR=3.899(1.104-13.780)
Carotid intima-media thickness	1 [Zhang 2020]	OR=9.53(1.47-61.72)
Common carotid artery dissection	1 [Zhao 2021]	OR=3.835(1.469-10.012)
Bovine aortic arch	1 [Dumfarth 2018]	OR=2.33(1.086 -4.998)
Preoperative malperfusion	1 [Dumfarth 2018]	OR=2.536(1.238-5.194)
Retrograde tears in the ascending aorta	3 [Zhao 2018; Zhao 2020; Zhao 2021]	OR=6.67(3.23-13.79)
Aortic arch tear	2 [Zhao 2020; Zhao 2021]	OR=5.82(1.98-17.10)
Impaired perfusion in the right carotid artery	1 [Dumfarth 2018]	OR=2.17(0.957-4.92)
Preoperative limb ischemia	1 [Xue 2021]	OR =2.814(1.258-6.298)
Salvage surgery	1 [Xue 2021]	OR=3.253(1.125-9.404)
Preoperative EUROSCORE score	1 [Haldenwang 2012]	OR=1.158(1.00-1.34)
Total leukocyte count	1 [Xu 2020]	OR=1.164(1.014-1.284)
Preoperative platelet count	1 [Yu 2019]	OR=0.988(0.978-0.999)
D-dimer	1 [Xu 2020]	OR=1.027(1.009-1.046)
Hypertension	2 [Ghoreishi 2020; Jiang 2018]	OR=1.38(1.13-1.69)
End-stage renal disease	1 [Xue 2021]	OR=6.957(1.301-37.2)
Hypotension	1 [Zhao 2020]	OR=10.173(1.381-74.944)
Intraoperative extracorporeal circulation duration	3 [Ghoreishi 2020; Wang 2020; Xu 2020]	OR=1.01(1.00-1.02)
Aortic occlusion duration	1 [Haldenwang 2012]	OR=1.014(1.00-1.03)
Circulatory arrest duration	1 [Li 2020]	OR=3.201(1.001-7.425)
Axillary artery cannulation	1 [Ghoreishi 2020]	OR=0.60(0.49-0.73)
Aortic cannulation	1 [Ghoreishi 2020]	OR=0.73(0.58-0.91)
Innominate artery cannulation	1 [Ghoreishi 2020]	OR=0.52(0.34-0.81)
Total arch replacement	1 [Ghoreishi 2020]	OR=1.28(1.02-1.61)
Retrograde perfusion	1 [Ghoreishi 2020]	OR=0.75(0.61-0.93)
Low-flow cerebral perfusion	1 [Xue 2021]	OR=2.139(1.014-4.515)
Prolonged intraoperative haemostasis duration	1 [Yu 2019]	OR=1.043(1.009-1.078)
Length of surgery	1 [Zhao 2020]	OR=1.021(1.003-1.039)
Postoperative low cardiac output	1 [Li 2020]	OR=2.812(2.425-5.736)

Table 2.

**Postoperative factors:** The postoperative factor involved in the included studies was postoperative low cardiac output. Results showed that postoperative low cardiac output (OR, 2.812; 95% CI, 2.425–5.3736) was a risk factor for PND after TAAD (Table 2).

**Sensitivity analysis and publication bias test:** Sensitivity analyses were performed by excluding each of the included exposure factors individually, and the results were more

stable. A funnel plot analysis of factors that was included in more studies, such as age and preoperative PND, showed no publication bias. (Figure 6)

## DISCUSSION

A total of 20 studies were included in this study, of which one was a prospective cohort study [Zhang 2020] and the



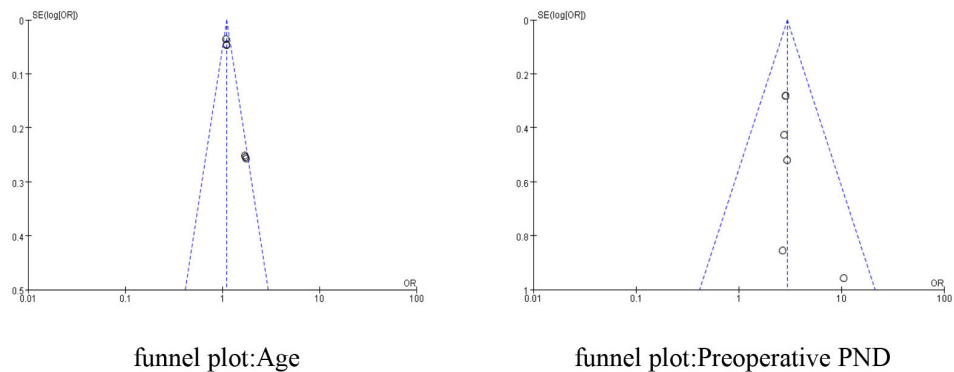


Figure 6. Funnel plot

Supplementary Table 1.

- 
- #1 aortic dissection[Title/Abstract]
  - #2 Type B Aortic Dissection[Title/Abstract]
  - #3 #1 NOT #2
  - #4 permanent neurological dysfunction[Title/Abstract] OR neurological dysfunction [Title/Abstract] OR neurological complication[Title/Abstract] OR neurological injury [Title/Abstract] OR neurological impairment[Title/Abstract] OR cerebral complication\* [Title/Abstract] OR central Nervous System Complication[Title/Abstract] OR neurological adverse outcomes[Title/Abstract]
  - #5 "Stroke"[Mesh]
  - #6 cerebrovascular accident\*[Title/Abstract] OR Cerebrovascular Apoplexy[Title/Abstract] OR Brain Vascular Accidents[Title/Abstract] OR Apoplexy[Title/Abstract]
  - #7 #5 OR #6
  - #8 "Brain Ischemia"[Mesh]
  - #9 brain ischemia\*[Title/Abstract] OR brain hemorrhage[Title/Abstract] OR Ischemic Encephalopath\*[Title/Abstract] OR (Cerebral Ischemia\*[Title/Abstract])
  - #10 #8 OR #9
  - #11 "Hypoxia-Ischemia, Brain"[Mesh]
  - #12 Hypoxic ischemic encephalopath\*[Title/Abstract] OR (Brain Hypoxia-Ischemia\*[Title/Abstract] OR Cerebral Hypoxia Ischemia\*[Title/Abstract]) OR (Brain Anoxia-Ischemia\* [Title/Abstract] OR Cerebral Anoxia Ischemia\*[Title/Abstract])
  - #13 #11 OR #12
  - #14 "Paraplegia"[Mesh]
  - #15 paraplegia\*[Title/Abstract] OR Cerebral Paraplegia\*[Title/Abstract] OR Spinal Paraplegia\*[Title/Abstract]
  - #16 #14 OR #15
  - #17 #4 OR #7 OR #10 OR #13 OR #16
  - #18 "Risk Factors"[Mesh]
  - #19 risk factor[Title/Abstract] OR Risk\*[Title/Abstract] OR Predictor[Title/Abstract] OR (predictive factor[Title/Abstract] OR influence factor[Title/Abstract] OR correlat\*[Title/Abstract] OR predict\*[Title/Abstract])
  - #20 #18 OR #19
  - #21 #3 AND #17 AND #20

rest were case-control studies. The included studies all had a definite diagnosis of type A arterial dissection, continuously enrolled subjects, and stated the time period of inclusion. Each study had a definite diagnosis of postoperative PND. Because of the numerous risk factors for PND after TAAD, most studies considered risk factors related to the patients' preoperative general information, disease history, and intraoperative extracorporeal circulation. Only independent risk factors from the multivariate analysis were included in this study, and the findings were authentic and reliable. The NOS score was in the range of 6–9, and six studies had 9 points each, suggesting high quality.

A total of 11382 Stanford type A aortic dissection patients and 1321 postoperative PND patients were included in the 20 studies. The study results showed that preoperative risk factors included age, preoperative PND, retrograde tearing in the ascending aorta. The risk of preoperative PND increased by 2.95-fold, and that of a retrograde tear in the ascending aorta increased by 6.67-fold. These are the main risk factors for PND after TAAD.

The results of this study are inconsistent with those of Liu et al. [Liu 2020]. This may be due to the following reasons: i) Liu et al. [Liu 2020] study included patients with postoperative neurological complications, including permanent and transient neurological complications, while this study only included patients with permanent postoperative neurological dysfunction; and (ii) the Liu et al. [Liu 2020] study included 3,438 patients with acute TAAD, and the present study included 11382 TAAD patients. Based on current evidence, there are numerous risk factors for postoperative PND in patients with TAAD, and it is recommended that clinical staff use the major risk factors to identify patients with postoperative PND early and provide evidence for their prevention. The International Registry of Acute Aortic Dissection was established in 1996 >7300 cases have been included from >51 sites in 12 countries, for the purpose of enrolling a large number of patients at a number of aortic centers to assess the presentation, management, and outcomes of AAD, and providing optimal diagnosis and management [Evangelista 2018]. We suggest a study on the risk factors of postoperative PND in patients with TAAD.

**There are some limitations to this study:** (i) Study patients included TAAD and acute TAAD patients, which were not analyzed separately because of the limited inclusion of risk factors in the meta-analysis; (ii) The number of independent risk factors included in the 20 studies was 34 but only eight were included in the final meta-analysis; (iii) As the incidence of TAAD patients was 5–10/100,000, only five centers in the included papers were foreign, while the rest were all from China, suggesting International Registry of Acute Aortic Dissection Inclusion of the Chinese population; (iv) Most of the included studies were retrospective case controls. Future prospective large multicenter studies should be conducted that considers primary and secondary confounding factors to establish a predictive model for PND after TAAD surgery and provide a basis for its early identification and management.

The results of this study suggest that age, preoperative PND, a retrograde tear in the ascending aorta, and

intraoperative extracorporeal circulation time are independent risk factors for the development of TND after TAAD. Given these limitations, further studies are needed.

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