

## Original Article

# Effect of hemodynamic changes on the risk of intracranial aneurysm rupture: a systematic review and meta-analysis

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**Abstract:** Objective: In this study, the hemodynamic parameters of ruptured intracranial aneurysms (IAs) in various studies were summarized and analyzed to provide predictive parameters for IA rupture in clinical work. Methods: We searched PubMed, Web of science, Embase, and Cochrane databases for articles published before December 2021 to collect data on hemodynamic parameters associated with IA rupture. Differences in wall shear stress (WSS), oscillatory shear index (OSI), and low wall shear stress area (LSA) between ruptured and unruptured IAs in the literature were summarized and analyzed, and the standardized mean difference (SMD) of 95% CI was calculated by Review Manager 5.3. Results: By searching and screening the literature, this meta-analysis included 17 studies comprising 1,373 IA patients. In the ruptured aneurysm group, the level of WSS decreased significantly, while OSI and LSA increased obviously. Conclusion: Low WSS, high OSI, and high LSA are closely related to the rupture of IAs, indicating the role of WSS, OSI, and LSA as important hemodynamic parameters for predicting the rupture of IAs in clinical work.

**Keywords:** Intracranial aneurysm, meta-analysis, rupture, wall shear stress

## Introduction

As imaging diagnosis technology constantly develops, the diagnosis rate of intracranial aneurysms (IAs) has gradually increased, with a reported incidence of unruptured IAs of about 3.7% in the Chinese population [1]. IA is a main inducement of non-traumatic subarachnoid hemorrhage. With the gradual increase of volume, IAs will compress local nerves and brain tissues, resulting in headache, dizziness, and blurred vision, which will have an adverse impact on patients' daily life [2]. In addition, rupture of IAs will seriously endanger the patient's life. At present, the treatment of IAs is a great challenge for clinicians, as it is difficult to make a decision to perform intervention surgery or follow-up. Since IAs grow over time, the specific intervention often depends on their size and location. While small IAs may have the risk of rupture, some relatively large ones may gradually tend to be stable. In addition, surgical

treatment may cause related complications and even death [3]. Therefore, clinicians need to make an individualized assessment of the rupture risk in IA patients, so as to decide whether to take intervention measures.

Many risk factors, such as age, genetic factors, hypertension, tumor shape, and location, have been found to be associated with IA rupture. In addition, as one of the important mechanisms of IA rupture, hemodynamic factors have attracted increasing attention of clinical workers. At present, many studies have detected the hemodynamic parameters of IA patients by computational fluid dynamics (CFD) technology and analyzed their correlation with IA rupture. However, due to the small scale of these studies and inconsistent results, their guiding role for clinical treatment is limited.

For example, there are currently two theories about the effect of wall shear stress (WSS), the

most frequently studied hemodynamic parameter in IAs, on IA rupture. Some scholars believe that high WSS is more likely to adversely affect vascular wall remodeling and aggravate endothelial injury [4, 5]. On the contrary, some studies have found that low WSS can easily lead to local blood flow stagnation in IAs, which will cause local inflammatory factor aggregation and endothelial dysfunction, contributing to aneurysmal wall degeneration [6, 7]. The conflicting conclusions may confuse clinical research and treatment of IAs.

In view of the inconsistent conclusions of previous studies and the complexity of hemodynamics in the occurrence of IAs, this meta-analysis aims to summarize and analyze the data of previous studies, so as to determine the hemodynamic parameters most relevant to IA rupture and provide guidance for clinical treatment.

## Methods and materials

### *Data retrieval and collection*

We searched PubMed, web of science, Embase, and Cochrane databases for relevant literature with the following keywords: “aneurysm”, “ruptured aneurysm”, “brain”, “internal”, “computational fluid dynamics”, “wall shear stress”, “low shear area”, and “oscillatory shear index”. All eligible papers published from January 2000 to December 2021 were searched. Two personnel with more than 3 years of retrieval experience were responsible for literature retrieval.

### *Inclusion criteria*

(1) Prospective and retrospective studies; (2) Language: English; (3) Sample size:  $\geq 10$  subjects; (4) Subjects with ruptured or unruptured IAs; (5) The studies including relevant hemodynamic parameters (WSS, low wall shear stress area [LSA], oscillatory shear index [OSI], etc.).

### *Exclusion criteria*

(1) Animal experimental research; (2) Case reports, reviews, comments, or guidelines; (3) Study on non-IA; (4) Inability to get complete data; (5) Duplicate literature.

### *Quality evaluation of included literature*

Using the Newcastle-Ottawa Scale (NOS) [8], two researchers evaluated the quality of the

included literature. Studies with a NOS score  $\geq 6$  points were defined as high-quality research.

### *Data extraction*

For the literature included in the study, we extracted the author(s), year of publication, age, number of samples, aneurysm type, volume matching, time-point, mean WSS, Max WSS, min WSS, OSI, and LSA. If necessary, the author(s) of the article were contacted to obtain more detailed data.

### *Publication bias of included literature*

Funnel plot was used to evaluate the publication bias of the included studies.

### *Statistical analysis*

Revman 5.3 was used for meta-analysis. Among hemodynamic parameters, the continuous variables were expressed as standardized mean difference (SMD) and 95% confidence interval (CI), and a forest plot was generated by the fixed effect model. For each meta-analysis, Cochran Q and  $I^2$  were used to evaluate the heterogeneity of the study. If the combined SMD of 95% CI in the meta-analysis didn't overlap with 0, the effect of the outcome measure was considered to be statistically significant.

## Results and discussion

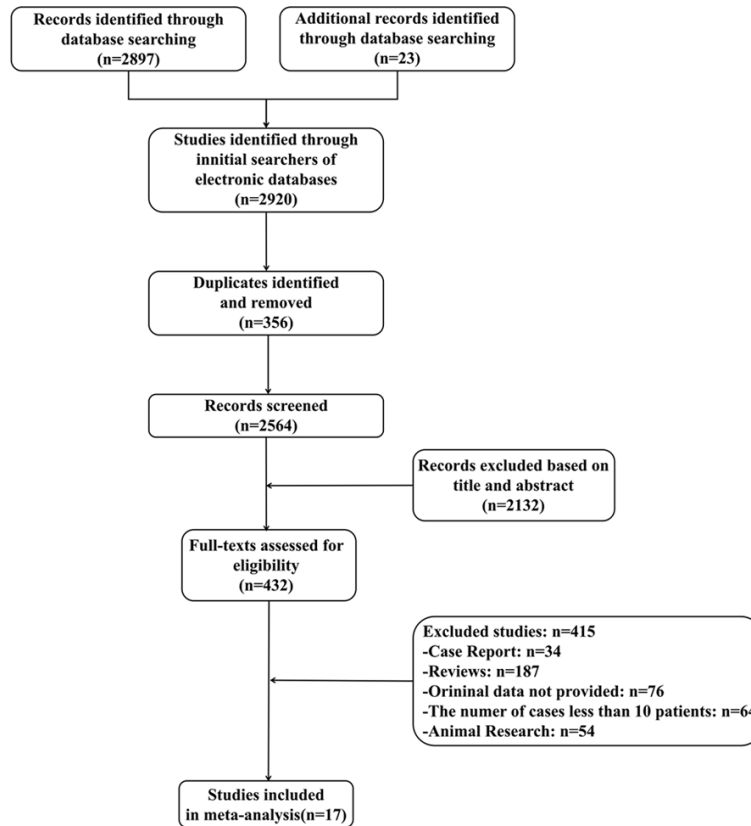
### *Literature search*

A total of 2,920 relevant literature records were screened by the keywords used. After deleting duplicate literature, we screened the remaining 2,564 records by title and abstract and excluded 2,132. The remaining 432 studies were further screened, among which 415 records, including 34 case studies, 177 reviews, 66 studies with insufficient data, 54 cases with less than 10 patients, and 54 animal studies, were further excluded. Finally, 17 studies were included, with a total of 1,373 IA patients [4-7, 9-21]. Of these, 6 studies had a sample size of more than 100 patients. The retrieval process is presented in **Figure 1**, and the research characteristics are shown in **Table 1**.

### *Quality evaluation*

After evaluating the literature quality with the NOS (NOS), it was found that the proportion of literature with a NOS score  $>6$  points was

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**Figure 1.** Flow diagram of data retrieval and collection.

94.12% (8 points for 6 items, 7 points for 5 items and 6 points for 5 items), suggesting that the included studies met the high quality standard, as shown in **Table 1** (continued). After the generation of the risk of bias graph/summary of the included studies, we found that the low bias risk mainly focused on the representativeness of “exposed group, non-exposed group” and “outcome indicators of positive observation”, while the bias risk was not clear in “determining exposure factors” and “the integrity of follow-up”, and the high bias risk was mainly concentrated in “long enough follow-up time” (**Figure 2**).

## Correlation between changes of WSS and IA rupture

WSS mainly refers to the longitudinal shear force produced by the horizontal flow of blood flow on the arterial wall, which is the key factor influencing IA rupture. In order to further explore the correlation between WSS level and IA rupture, we included 14 studies with 15 groups of average WSS data. The study found that the

average WSS was closely related to IA rupture. The average WSS level in the rupture group was relatively low, and its combined SMD was -0.38 (95% CI: 0.50 to -0.26;  $P < 0.001$ ) (**Figure 3A**). Besides, we further explored the correlation of max and min WSS with IA rupture. By summarizing the max WSS data of 8 groups in 7 studies, it was found that the max WSS was not significantly associated with IA rupture, and its combined SMD was 0.05 (95% CI: -0.09 to 0.20;  $P = 0.48$ ) (**Figure 3B**). After summarizing the min WSS data of 6 studies, we observed that the min WSS decreased significantly in IA rupture group, and its combined SMD was -0.29 (95% CI: -0.47 to -0.11;  $P = 0.002$ ) (**Figure 3C**).

## Correlation between changes of OSI and IA rupture

OSI can be used to reflect the change of blood flow direction and intensity in IAs, which is helpful for effective evaluation of the stability of local blood flow. Through the summary and analysis of the data included in 13 studies, we found that OSI level was higher in the rupture group, and its combined SMD was 0.33 (95% CI: 0.20 to 0.46;  $P < 0.001$ ) (**Figure 4**). Hence, greater OSI will repeatedly damage the intima of the tumor wall, eventually leading to IA rupture.

## Correlation between changes of LSA and IA rupture

LSA can reflect the area of the whole tumor wall surface less than 10% of mean WSS, which can further evaluate the effect of WSS on IA rupture. After a comprehensive analysis of the data from 12 studies, it was found that LSA was an important risk factor for IA rupture, with 11 of the 12 studies indicating a positive correlation between high LSA and aneurysm rupture, and its combined SMD was 0.66 (95% CI: 0.52 to 0.80;  $P < 0.001$ ) (**Figure 5**).

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**Table 1.** IA patients' basic information and aneurysms hemodynamic parameters of included studies

author, year	mean age (year)	aneurysm location	total patients		time- point	vm	mean WSS (pa)			max WSS (pa)			min WSS (pa)		
			rup	Unrup			rup	unrup	p	rup	unrup	p	rup	unrup	p
chung [4], 2017	nr	pcom	145	168	nr	no	24.17±23.21	22.34±20.16	0.59	341.3±299.9	231.54±172.1	<0.001	0.29±0.74	0.64±1.39	0.02
duan [6], 2016	60.5 (43-86)	pcom	6	24	nr	yes	0.433±0.242	0.901±0.322	0.005	nr	nr		nr	nr	
fan [7], 2015	60.6 (46-77)	mca, pcom	16	16	ed	nr	7.43±4.03	11.29±5.41	0.029	50.84±25.8	53.31±17.82	0.725	0.08±0.15	0.18±0.52	0.056
lauric [9], 2014	61.4 (38-77)	ica	9	9	ed	yes	0.161±0.111	0.309±0.188	0.06	3.331±4.403	5.003±4.231	0.45	0.001±0.002	0.31±0.033	0.03
li [10], 2020	nr	ica	23	133	ta	nr	1.0412±0.7201	1.2931±1.1705	0.534	3.9772±4.6113	5.8006±21.8439	0.69	0.9584±0.7999	1.046±0.914	0.816
liu [11], 2016	60.33±16.56	ica	3	8	es	yes	0.3±0.06	0.48±0.13	0.048	nr	nr	nr	nr	nr	nr
liu [12], 2019	57.7±6.4	ica, mca, acom	5	15	es	no	2.1±0.9	2.3±1.1	0.698	nr	nr	nr	nr	nr	nr
lu [13], 2011	54.4 (42-66)	aca, mca	9	9	ta	nr	6.49±3.48	9.8±4.12	nr	nr	nr	nr	nr	nr	nr
lv [14], 2016	58 (52-64)	pcom	33	21	nr	nr	0.4563±0.6037	0.7964±0.2942	0.018	nr	nr	nr	nr	nr	nr
miura [15], 2013	nr	mca	43	63	nr	yes	7.463±6.1894	9.6524±6.0317	0.0001	nr	nr	nr	nr	nr	nr
perera [16], 2020	nr	ica, pcom, acom, mca, ba	10	38	ta	yes	1.157±0.41	1.353±0.39	0.173	2.868±1.01	3.003±1.04	0.714	0.331±0.134	0.416±0.15	0.103
qiu [5], 2017	56.9±9.43	mca, pcom, aca, ca, oa	41	31	ta	nr	1.96±1.3	3.33±1.45	0.028	13.687±9.15	12.412±5.98	0.596	nr	nr	nr
							7.85±3.98	7.14±3.08	0.655	9.08±6.64	8.19±3.69	0.72			
xiang [17], 2011	nr	ica, mca, pcom, pca, acom, aca, ba, pica	38	81	nr	yes	0.33±0.28	0.68±0.4	<0.001	2.71±2.2	3.87±1.91	0.0002	nr	nr	nr
xu [18], 2018	nr	ica	10	25	ed	no	5.45±5.05	5.64±2.86	0.887	nr	nr	nr	0.5±0.5	0.59±0.4	0.575
yuan [19], 2020	50.67±7.94	pcom, oa, mca	12	12	es	nr	0.54±0.21	0.75±0.19	<0.001	nr	nr	nr	nr	nr	nr
yuan [20], 2021	58.18±11.22	pcom	72	72	ta	nr	8.2±3.36	11.56±5.28	<0.001	nr	nr	nr	nr	nr	nr

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zhang [21], 2016	58.5±10.5	pcom	108	65	ta	yes	0.55±0.23	0.69±0.25	<0.001	1.97±0.51	2.05±0.43	0.311	nr	nr	nr
Author, year	OSI			LSA (%)			NOS score								
	Rup	Unrup	P	Rup	Unrup	P									
Chung [4], 2017	0.017±0.015	0.013±0.014	<0.001	59.63±30.46	52.32±31.91	0.05	8								
Duan [6], 2016	0.019±0.040	0.017±0.026	0.897	0.063±0.203	0.0005±0.013	0.01	6								
Fan [7], 2015	0.0219±0.0189	0.0151±0.0234	0.319	5.83±21.27	0.41±1.56	0.020	8								
Lauric [9], 2014	NR	NR	NR	NR	NR	NR	5								
Li [10], 2020	0.01775±0.07042	0.01277±0.03591	0.912	NR	NR	NR	6								
Liu [11], 2016	0.05±0.04	0.04±0.03	1	12.39±4.63	6.28±5.16	0.085	8								
Liu [12], 2019	0.0076±0.003	0.0039±0.0031	0.031	0.35±0.15	0.48±0.13	0.028	7								
Lu [13], 2011	0.0879±0.0764	0.0183±0.0191	0.008	12.2±18.08	3.96±6.91	0.015	7								
Lv [14], 2016	0.02±0.0155	0.01±0.0159	NR	0.0442±0.062	0.0036±0.008	0.008	7								
Miura [15], 2013	0.0196±0.0152	0.0149±0.0108	0.00891	NR	NR	NR	6								
Perera [16], 2020	0.12 (0.08)	0.075 (0.08)	0.141	NR	NR	NR	6								
	0.026 (0.02)	0.011 (0.01)	0.008												
Qiu [5], 2017	NR	NR	NR	0.34±0.308	0.093±0.125	0.015	8								
Xiang [17], 2011	0.016±0.031	0.0035±0.0044	<0.0001	0.38±0.31	0.1±0.21	<0.0001	7								
Xu [18], 2018	0.015±0.016	0.016±0.019	0.911	21.21±25.31	6.16±16.5	0.049	8								
Yuan [19], 2020	0.026±0.009	0.023±0.01	0.136	0.1783±0.109	0.0295±0.0503	0.002	7								
Yuan [20], 2021	0.025±0.015	0.023±0.01	0.452	9.8±7.37	2.89±2.73	<0.001	8								
Zhang [21], 2016	NR	NR	NR	NR	NR	NR	6								

Note: PCOM: posterior communicating artery; MCA: middle cerebral artery; ICA: internal carotid artery; ACOM: anterior communicating artery; ACA: anterior cerebral artery; BA: basilar artery; CA: carotid artery; OA: ophthalmic artery; PCA: posterior cerebral artery; PICA: posterior inferior cerebellar artery; NR, no report; TA, time averaged; ED, end-diastolic; ES, end-systolic.

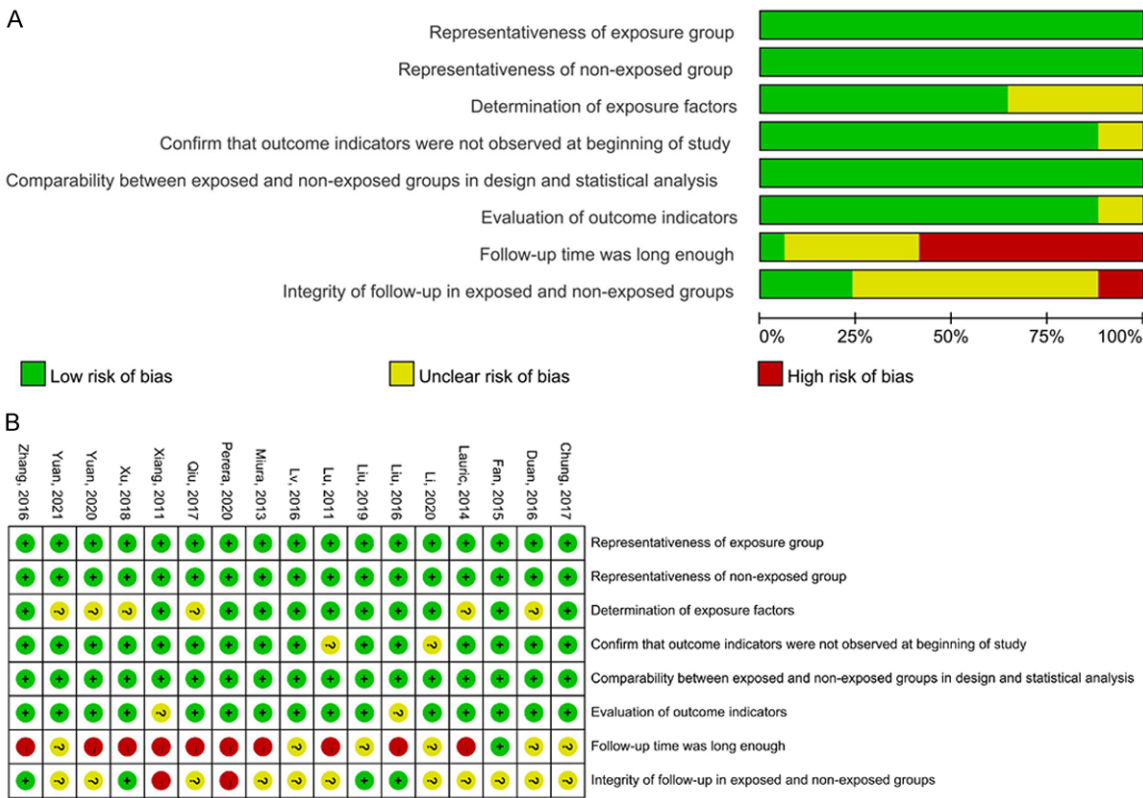


Figure 2. The risk of bias graph (A) and bias summary (B) of included studies.

Publication bias

We further evaluated whether the included studies were biased through funnel plot. It was found that the mean WSS (Figure 6A), OSI (Figure 6B), and LSA (Figure 6C) were basically symmetrically distributed, indicating no obvious evidence of publication bias.

Discussion

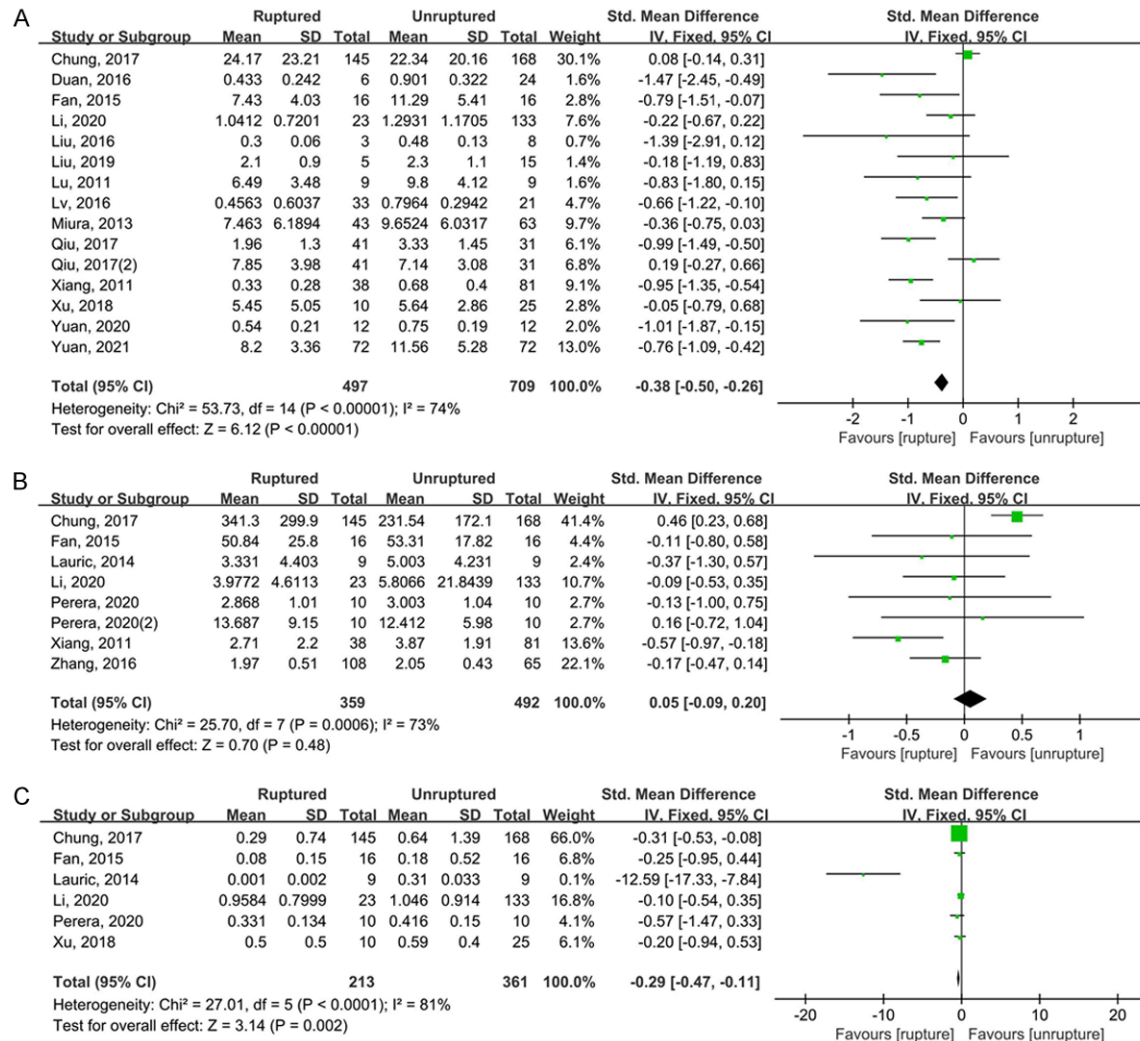
Hemodynamics is an important risk factor affecting the formation and rupture of IAs. Changes in blood flow within the aneurysm creates pressure on specific part of the aneurysm wall, resulting in endothelial cell damage and ultimately IA rupture [9]. At present, the study of hemodynamic parameters in aneurysms through CFD is a hot spot in clinical research, which can effectively analyze the blood flow parameters of various parts of aneurysms and understand the hemodynamic changes of ruptured aneurysms. The comparative analysis of various blood flow parameters helps doctors to comprehensively evaluate the risk of aneurysm rupture, thus effectively guiding the

choice of aneurysm therapy [10]. At present, there are many clinical studies on the correlation between hemodynamic parameters and IA rupture. However, different indicators are detected in these studies, with inconsistent conclusions. Therefore, we summarized and analyzed the correlation between hemodynamic parameters and IA rupture in various studies to find representative indicators, so as to better guide clinical work.

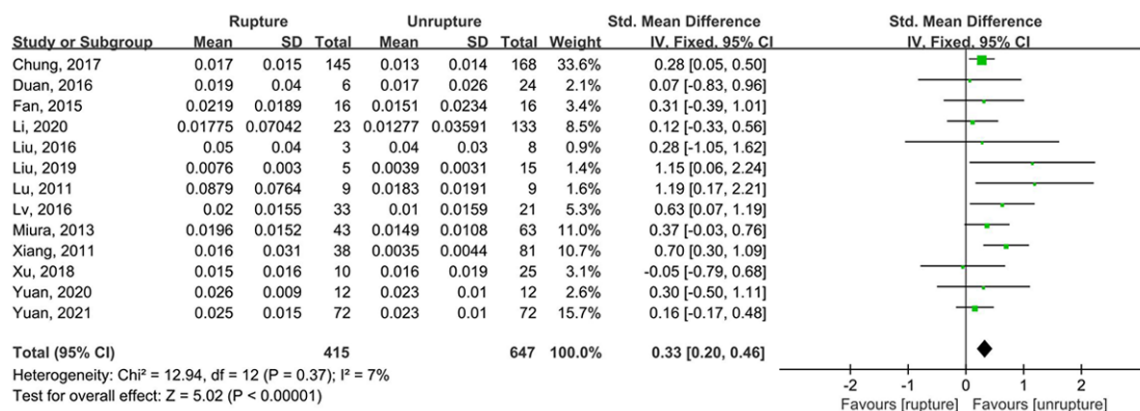
WSS is closely related to IA rupture, and its effect in aneurysms has been widely studied. A large retrospective study with about 200 cases showed an association between low and high WSS and aneurysm rupture status, a seemingly contradictory phenomenon that may simply reflect the double-sided nature of aneurysm wall remodeling. WSS can effectively maintain the shape of the aneurysm wall, and the change of its value will increase the risk of aneurysm rupture. After a comprehensive analysis of the data of mean WSS in the aneurysm rupture group of 14 studies, it was found that only two groups of data indicated elevated mean WSS in the rupture group, while the rest



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**Figure 3.** Meta-analysis of WSS between ruptured and unruptured aneurysms. A. Forest plot of mean WSS. B. Forest plot of max WSS. C. Forest plot of min WSS. Wall shear stress (WSS).

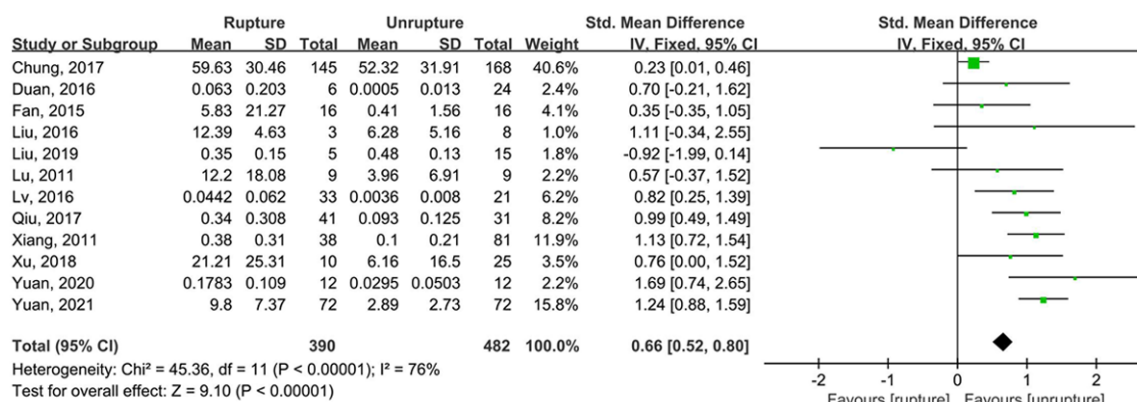


**Figure 4.** Meta-analysis of OSI between ruptured and unruptured aneurysms.

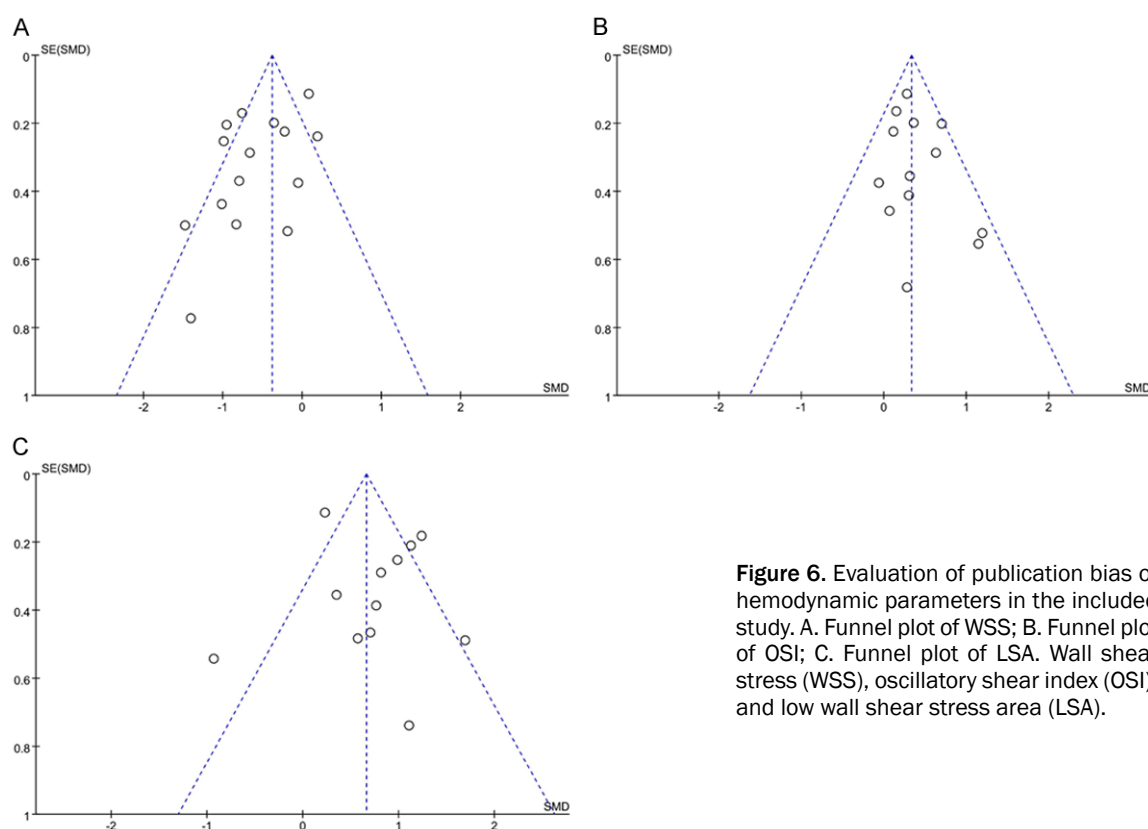
suggested a low mean WSS in ruptured IAs compared with unruptured IAs, suggesting that

IA rupture is closely related to WSS insufficiency. The reason maybe that low WSS will lead to

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**Figure 5.** Meta-analysis of LSA between ruptured and unruptured aneurysms.



**Figure 6.** Evaluation of publication bias of hemodynamic parameters in the included study. A. Funnel plot of WSS; B. Funnel plot of OSI; C. Funnel plot of LSA. Wall shear stress (WSS), oscillatory shear index (OSI), and low wall shear stress area (LSA).

the dysfunction of local vascular endothelial cells that will affect their barrier function, which causes the invasion of harmful substances in the blood into the vascular wall, resulting in the degeneration and fracture of elastic fibers in the tumor wall and finally causing the rupture of IAs. In addition, we found that the occurrence of IA rupture was not significantly associated with max WSS but was significantly associated with min WSS. By using CFD simulations,

Shojima et al. [22] and Jou et al. [23] found that IA rupture occurred not only at high values of hemodynamic parameters, but also at their low values, such as low values of WSS.

OSI is an important index reflecting the rapid change of blood flow direction in aneurysms. Through the comprehensive analysis of the data in 13 studies, we found decreased OSI levels in ruptured IAs in only one group of data,



while higher OSI levels in ruptured IAs compared with unruptured IAs in the rest. High OSI means that the direction of WSS in aneurysms is more likely to change, which will have a greater oscillatory effect on the tumor wall. After reaching a certain threshold, vascular endothelial cells will be damaged and collagen fibers will be exposed, resulting in platelet adhesion at the injury site and thrombosis, and finally inducing the rupture of aneurysms under the action of fibrinolytic reaction. Perera R et al. [16] identified in the multivariate analysis that OSI was the only significant biomarker for predicting aneurysm rupture risk. Meng et al. [24] also proposed that aneurysm wall degeneration induced by high OSI may be triggered by destructive remodeling mediated by inflammatory cells.

In addition, after a comprehensive analysis of 12 groups of data on the correlation between LSA and aneurysm rupture, we found that high LSA was an important risk factor for IA rupture. LSA mainly reflects the area of less than 10% mean WSS on the tumor surface. A higher value indicates a higher possibility of the aneurysm to be affected by low WSS, and consequently a higher likelihood of the endothelial cells to be damaged and fall off from the tumor wall, all of which results in the destruction of the integrity of the vascular wall and an increased risk of aneurysm rupture. The meta-analyses conducted by Can and Du showed significantly higher LSA in the ruptured IAs [25]. Zhang et al. [26] also noted that the ruptured aneurysms had significantly higher LSA than the unruptured aneurysms.

This study mainly analyzed the influence of hemodynamic parameters on IA rupture. However, many studies include aneurysms in multiple locations, making it difficult to analyze the hemodynamic parameters of aneurysms in different locations. In addition, the risk of IA rupture increases with the patient's age and tumor diameter. Subgroup analysis of different ages and tumor diameters is not carried out in this study, so more data should be continuously collected in the later stage for a more detailed summary.

## Conclusion

In conclusion, low mean WSS, low min WSS, high OSI, and high LSA are important risk fac-

tors for IA rupture, which can help predict the risk of aneurysm rupture in clinic to better guide clinical treatment.

## Disclosure of conflict of interest

None.

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