Risk Factors for Intracranial Aneurysm Rupture: A Systematic Review

Rachel Kleinloog, MD*
Nikki de Mul, MD*
Bon H. Verweij, MD, PhD*
Jan Andries Post, PhD‡
Gabriel J. E. Rinkel, MD, FRCPE*
Ynte M. Ruigrok, MD, PhD*

*Brain Center Rudolf Magnus, Department of Neurology and Neurosurgery, University Medical Center Utrecht, Utrecht, The Netherlands; ‡Cell Biology, Department of Biology, Science Faculty, Utrecht University, Utrecht, The Netherlands

Correspondence:
Rachel Kleinloog,
Brain Center Rudolf Magnus,
Department of Neurology and Neurosurgery, G. 03.232,
University Medical Center Utrecht,
Heidelberglaan 100,
3584 CX Utrecht, The Netherlands.
E-mail: rachelkleinloog@gmail.com

Received, August 24, 2016.
Accepted, April 26, 2017.
Published Online, May 11, 2017.

BACKGROUND: Intracranial aneurysm rupture prediction is poor, with only a few risk factors for rupture identified and used in clinical practice.
OBJECTIVE: To provide an overview of all the risk factors (including genetic, molecular, morphological, and hemodynamic factors) that have potential for use in clinical practice.
METHODS: We systematically searched PubMed and EMBASE and focused on factors that can be easily assessed in clinical practice, might be used for rupture prediction in clinical practice, and/or are potential targets for further research. Studies were categorized according to methodological quality, and a meta-analysis was performed, if possible.
RESULTS: We included 102 studies describing 144 risk factors that fulfilled predefined criteria. There was strong evidence for the morphological factors irregular shape (studied in 4 prospective cohort studies of high-quality, pooled odds ratio [OR] of 4.8 [95% confidence interval 2.7-8.7]), aspect ratio (pooled OR 10.2 [4.3-24.6]), size ratio, bottleneck factor, and height-to-width ratio to increase rupture risk. Moderate level of evidence was found for presence of contact with the perianeurysmal environment (pooled OR 3.5 [1.4-8.4]), unbalanced nature of this contact (pooled OR 17.8 [8.3-38.5]), volume-to-ostium ratio, and direction of the aneurysm dome (pooled OR 1.5 [1.2-1.9]).
CONCLUSION: Irregular aneurysm shape was identified as a risk factor with potential for use in clinical practice. The risk factors aspect ratio, size ratio, bottleneck factor, height-to-width ratio, contact with the perianeurysmal environment, volume-to-ostium ratio, and dome-direction should first be confirmed in multivariate analysis and incorporated in prediction models.

KEY WORDS: Intracranial aneurysm, Subarachnoid hemorrhage, Review

Neurosurgery 82:431–440, 2018 DOI:10.1093/neuros/nyx238 www.neurosurgery-online.com

Approximately, 3% of the population harbors an unruptured intracranial aneurysm.[1] Given the rising availability and quality of brain imaging, the number of incidentally discovered aneurysms is increasing.[2] Rupture of intracranial aneurysms results in aneurysmal subarachnoid hemorrhage (aSAH), a subset of stroke that has high case fatality and morbidity, and occurs at a relatively young age compared with other types of stroke.[3,4] The incidence of aSAH is only 9 per 100 000 person-years,[5] indicating that the majority of unruptured aneurysms will never rupture. It is important to identify risk factors for rupture to tailor preventive treatment to the aneurysms that are at high risk of rupturing.

The number of factors that have been assessed in cohort studies and influence the risk of rupture is limited. These are age, sex, history of hypertension or subarachnoid hemorrhage, aneurysm size, and aneurysm location.[6] Other factors that might predict aneurysm rupture include cigarette smoking[7] and a family history of aSAH.[8] These factors only explain a small proportion of the risk of rupture. Therefore, rupture risk prediction for individual patients is still poor, and consequently the search for new risk factors continues.

The aim of the current study was to systematically review the literature on risk factors for rupture to identify genetic, molecular,

ABBREVIATIONS: aSAH, aneurysmal subarachnoid hemorrhage; **CI,** confidence interval; **OR,** odds ratio; **WSS,** wall shear stress

Supplemental digital content is available for this article at neurosurgery-online.com.

morphological, and hemodynamic factors in addition to the factors currently used in clinical practice. We focused on factors that can be easily assessed in clinical practice and thus have the potential to be used for rupture prediction. In addition, we aimed to identify potential targets for further research, that is, re-evaluation of the risk factors in large high-quality studies and assessment of their independence in multivariate analysis followed by prediction model studies.

METHODS

For this systematic review, the PRISMA guideline was followed.

Search Strategy and Selection Criteria

We systematically searched the PubMed and EMBASE databases until February 2015 using different combinations of the keywords (or their synonyms): "unruptured," "intracranial," "aneurysm," or "rupture" (please see **Supplemental Digital Content 1** for the full electronic search strategy). To assess eligibility of the articles found, either N.M. or R.K. screened the titles and abstracts, and, if necessary, the full text, on inclusion and exclusion criteria. If eligibility of an article was questioned by N.M., the article was reviewed by R.K., and vice versa. Any disagreement was resolved by consulting a third reviewer (Y.M.R.). Reference lists of relevant articles were searched for additional publications by R.K. and N.M. until no further publications were found. We included studies that compared potential factors in (1) ruptured vs unruptured aneurysms; (2) growing vs stable aneurysms during follow-up; (3) unruptured aneurysms of different sizes. Hence, growth and size of the aneurysms were considered surrogate markers of rupture, because large aneurysms and growing aneurysms have a higher risk of rupture.[6,7] We categorized potential factors into genetic (eg, polymorphisms, mutations), molecular, morphological, and hemodynamic factors. Studies were excluded if they were (1) reviews of the literature, conference abstracts, letters, or case reports (with $\leq$5 cases), (2) analyzing only mycotic or fusiform aneurysms, (3) animal models, (4) mathematical models (except models based on patient-specific data of multiple aneurysms), or (5) in languages other than English, German, French, Italian, or Spanish. Last, we excluded studies when the risk factor(s) investigated could only be determined during or after treatment of the aneurysm (eg, intraoperative measurements or measurements in tissue samples of aneurysms obtained during surgery or at autopsy), because these factors cannot be used in the clinical decision-making of whether or not to perform a preventive treatment in unruptured aneurysms. Figure 1 shows a flow chart of the literature search with inclusion and exclusion criteria.

Data Extraction

We extracted the following data on the methodology of the article: (1) study design being cohort or case control design, prospective or retrospective, and consecutive cases or not, (2) the population included, (3) aim of the study, (4) outcome measure, (5) sample size, (6) data analysis, and (7) data presentation. We extracted the crude data and effect estimates (odds ratio [OR] or risk ratio, and hazard ratio, if applicable) for each factor separately. If an OR was not given, we calculated the OR and its 95% confidence interval (CI) from the crude data, if available. If none of these effect estimates was available and crude data were missing, we reported the mean and standard deviation between groups and the statistical significance of their difference, if available. If a certain risk factor was studied in the same patient population and reported upon in 2 or more different publications, we only used data from the most recent publication for further analysis. Data extraction was performed by R.K. and cross-checked by Y.M.R. (senior author).

Quality Assessment

Quality assessment of the studies was performed using an adapted version of a previously published methodological quality score[9] and modified for the topic of our review (Table 1).[6,10] Studies with scores between 10 and 15 were defined as high-quality studies, and studies with scores <10 were defined as low-quality studies. In addition, for each factor, we assessed the level of evidence for the association with aneurysm rupture by combining the consistency of the effect estimates in the different studies, the size of the effect estimates, and the methodological quality of the study. We categorized the factors as factors associated (both positive or negative) or not associated with rupture. Level of evidence was categorized into strong, moderate, low, or inconsistent level of evidence (Figure 2). The methodological quality and level of evidence was assessed by R.K. and cross-checked by Y.M.R. (senior author).

Potency of Risk Factors for Clinical Practice or Further Clinical Research

We used predefined criteria for selection of those risk factors associated (both positive and negative) with rupture that can be directly used in the risk prediction of rupture in clinical practice or have potential for use after further evaluation in multivariate analysis and incorporation into prediction models (Table 2). Also, we predefined criteria for selection of risk factors which association with rupture should first be further confirmed in larger studies of higher quality (Table 2). Factors not associated with rupture were not considered relevant for use in clinical practice nor as having potential for further clinical research.

Analyses

A formal meta-analysis was performed, if possible, by calculating a pooled OR with corresponding 95% CI for factors associated with rupture with a strong or moderate level of evidence assessed in studies that provided crude data and had limited heterogeneity in the definition for the risk factor under study. We applied a random effects model with the Mantel-Haenzsel method by using Review Manager version 5.3.[11] To assess heterogeneity of effects across the studies assessed in the meta-analysis, we used the Higgins I^2.[12] Little to moderate heterogeneity was defined as $I^2 \leq 60\%$ and substantial heterogeneity as $I^2 > 60\%$.

RESULTS

A total of 102 studies analyzing 28 812 aneurysms met our inclusion criteria (see the flow chart [Figure 1]). These studies reported on 144 different risk factors. Of these risk factors, 12 were genetic, 18 molecular, 59 morphological, and 55 hemodynamic risk factors. Twenty-five studies fulfilled our criteria of high quality. A table with an overview of the study characteristics, including study design, number of aneurysms included, representation of the investigated population, outcome measure, and the methodological quality score of the 102 included studies, is provided in **Supplemental Digital Content 2** (see **Table**) as are

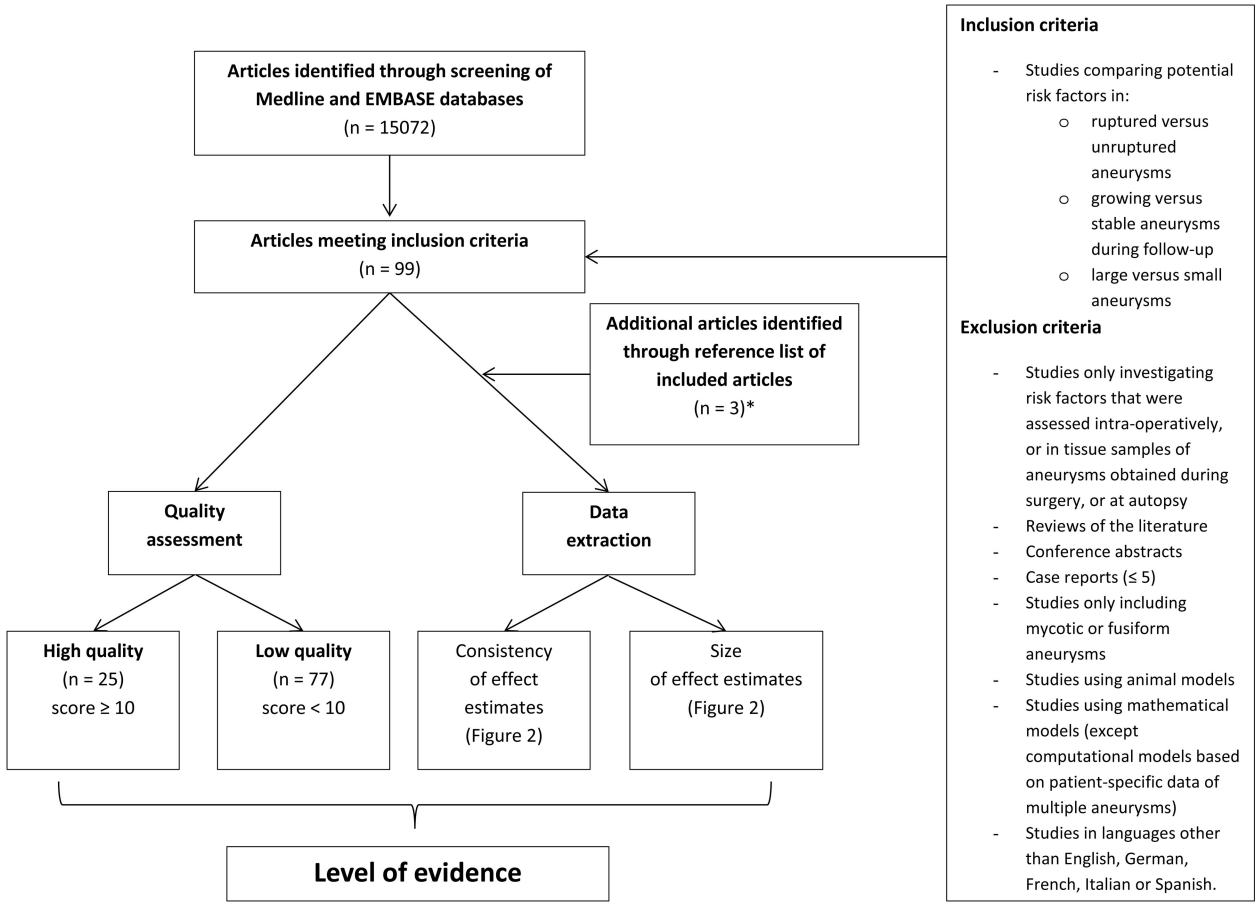

FIGURE 1. *Flow chart of the literature search with in- and exclusion criteria.*
** Three studies were identified through references of included articles and were not present in the original search.[16-18] The study by Nakaoka et al[16] was missed because it only used the word "ruptured" instead of the search term "rupture." Bilguvar et al[17] primarily analyzed genetic risk loci in aneurysms vs controls and did not report on their subanalysis on ruptured vs unruptured aneurysms (supplied in the **Supplemental Digital Content**) in their abstract and was therefore missed in the original search. The study by Parlea et al[18] was missed because the primary objective of the study was to characterize the geometry of simple-lobed aneurysms. Although a subanalysis of the differences in geometry between ruptured and unruptured aneurysms was included, they did not report this in their abstract.*

the references of the studies included. All risk factors with their effect estimates, the methodological quality scores, and the definitions of the factors are shown in **Supplemental Digital Content 3** and the definitions of the factors are shown in **Supplemental Digital Content 3** (factors associated with rupture), **Supplemental Digital Content 4** (factors not associated with rupture, and **Supplemental Digital Content 5** (factors with inconsistent evidence) (see Tables).

Factors Associated with Rupture

Strong Level of Evidence

Strong evidence for an increased risk of aneurysm rupture was found for 5 different morphological factors: (1) irregular shape of the aneurysm (pooled OR of 4.8, 95% CI 2.7-8.7 based on 10 studies; including multilobulated shape, and the presence of blebs, see Figure 3), (2) larger aspect ratio (pooled OR of 10.2, 95% CI 4.3-24.6 based on 3 studies; aneurysm height divided by the diameter of the neck, see Figure 3), (3) larger size ratio (aneurysm height divided by the [average] parent vessel diameter), (4) higher bottleneck factor (aneurysm width divided by the diameter of the neck), and (5) height-to-width ratio (aneurysm height divided by the aneurysm width; see Figure 3 and **Table**, **Supplemental Digital Content 3**). A pooled analysis of the ORs was not possible for the factors size ratio, bottleneck factor, and height-to-width ratio, either because of the use of different definitions (especially different or lack of cut-off values of ratio's) of the factors in different studies, because of the unavailability of

TABLE 1. Methodological Quality Score

Study methods		Points
Design	Prospective cohort of unruptured aneurysm until rupture/growth occurs (3)	3
	Retrospective cohort of unruptured aneurysm until rupture/growth occurs or a case control design with consecutive cases from a prospective database (2)	
	Case control design with consecutive cases from a retrospective database (1)	
	Nonconsecutive case-control design (0)	
Population	Representative group of patients with aneurysms[a]	3
	Baseline characteristics (age, gender, aneurysm size, aneurysm location) were described for all patients	1
Aim	The primary aim was to investigate the relationship between hemodynamic, morphological or genetic factors and aneurysm rupture, or surrogate markers of rupture: growth and size.	1
Outcome	Rupture as outcome measure (2)	2
	Growth as outcome measure (1)	
	Size as outcome measure (0)	
Size	• Longitudinal study design:	1
	—rupture as outcome: > 10 outcomes per risk factor studied (± 1% rupture risk per year, > 1000 patient years per risk factor)[6]	
	—growth as outcome: > 10 outcomes per risk factor studies (10% growth in 2 year, > 200 patient years per risk factor)[10]	
	• Cross-sectional study design:	
	> 10 outcomes (ruptured aneurysms) per risk factor studied (10 ruptured aneurysms per risk factor), or in case of size as surrogate marker 10 large aneurysms per risk factor.	
Data analysis and presentation		
	Either crude numbers provided, or odds ratio/relative risk/hazard ratio with 95% CI was provided (1)	2
	Both were provided (2)	
	Statistical analysis included multivariate analysis with inclusion of potential confounders, including aneurysm size and location.	1
	Statistical analysis included multivariate analysis, and the number of predictors studies was less than 1/10 of the total number of aneurysms	1
Total score	<10 = low quality; 10-15 = high quality	15

[a]A study population was considered not representative if a patient selection was made on age (other than adults), aneurysm size within the clinically relevant range (>3 mm), aneurysm location, number of aneurysms, treatment method or any treatment of the aneurysm (except for studies assessing the occurrence of growth or rupture during follow-up).

ORs or crude data to calculate ORs, or both. Heterogeneity was substantial across the studies assessing irregular shape (I^2 = 89%) and aspect ratio (I^2 = 94%). However, the heterogeneity test results can be influenced by poor precision of the estimate of between-study variance when analyzing only a small number of studies. The evidence for the risk factor irregular shape was based on >2 cohort studies of high quality with a pooled OR > 2.0 and therefore has high potential and should from now on be used in risk prediction of rupture in clinical practice (Table 2). Aspect ratio, size ratio, bottleneck factor, and height-to-width ratio have potential for use in clinical practice after further analysis (Table 2).

Moderate Level of Evidence

Four additional morphological factors were found to have a moderate level of evidence (**Table**, **Supplemental Digital Content 3**). First, the presence of contact of the aneurysm with surrounding anatomic structures, such as bone, dura mater, brain, vessels, or nerves was associated with rupture (pooled OR of 3.5, 95% CI 1.4-8.4 based on 3 studies, see Figure 3). Second, this contact was more often unbalanced (defined as an asymmetrical contact with the environment or contact with more than 1 anatomical structure) in ruptured aneurysms (pooled OR of 17.8, 95% CI 8.3-38.5 based on 2 studies, see Figure 3). Third, the volume-to-ostium ratio (ratio of the aneurysm volume to the area of the neck) was higher in ruptured aneurysms, and fourth, the downward/inferior direction of the aneurysm dome was also associated with rupture (pooled OR of 1.5, 95% CI 1.2-1.9 based on 2 studies, see Figure 3). A pooled analysis of the ORs in 2 or more high-quality studies was not possible for the factor volume-to-ostium ratio because of the absence of crude numbers or ORs. Heterogeneity was high for the factor presence of contact with the perianeurysmal environment (I^2 = 74%), while it was small for studies assessing the factor unbalanced contact with the perianeurysmal environment (I^2 = 0%) and the factor downward/inferior direction of the dome (I^2 = 0%). However, again, it should be emphasized that on analyzing only a small number of studies, the heterogeneity test results may be influenced by poor precision. All 4 factors have potential for use in clinical practice after further analysis.

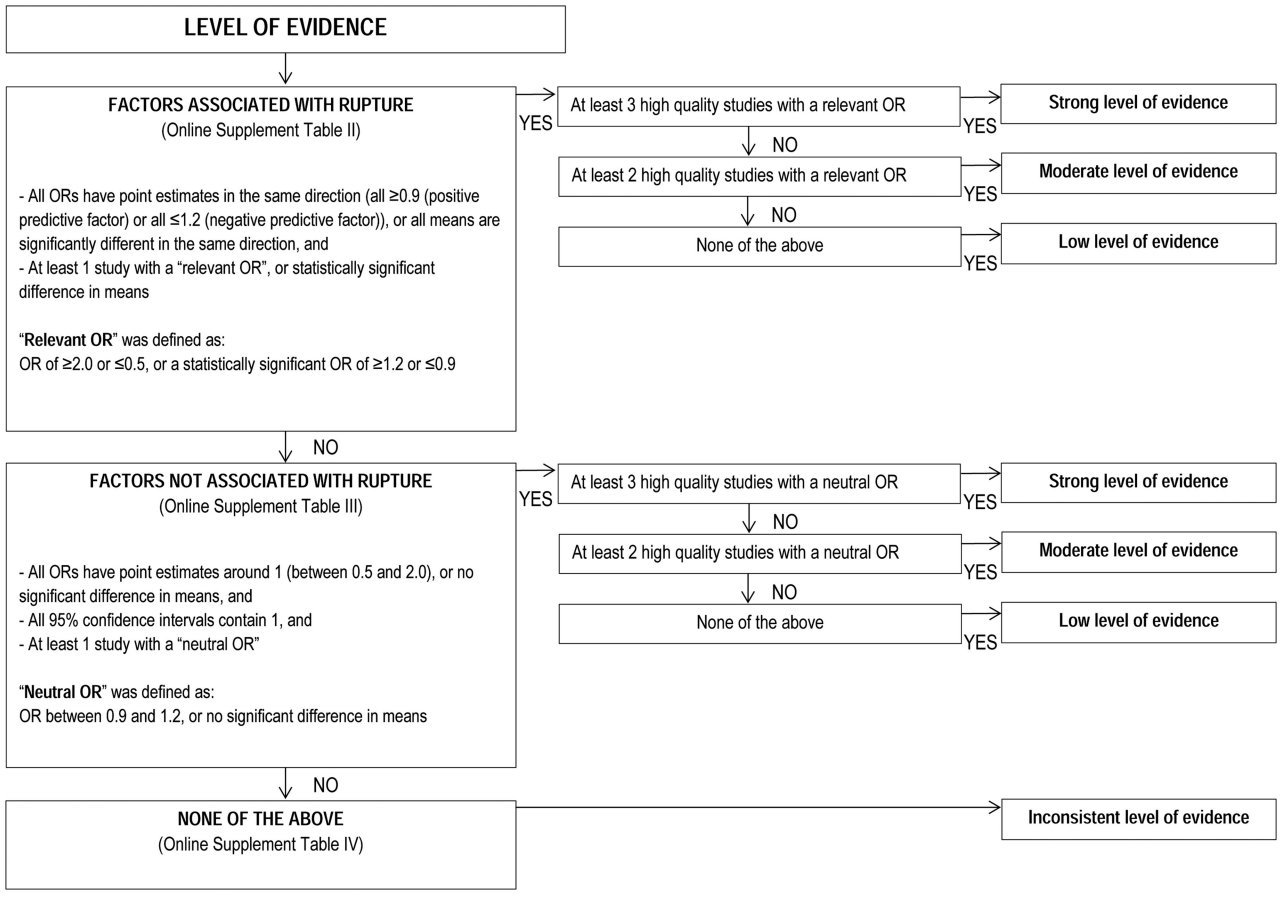

FIGURE 2. *Categories for level of evidence for each risk factor.*

TABLE 2. Potential of Risk Factors Associated with Rupture

Potential of risk factor	Criterion
To be directly used in risk prediction of rupture in clinical practice[a]	Factors with strong level of evidence including evidence from >2 cohort studies of high quality with a pooled OR >2.0.
To be used in risk prediction of rupture in clinical practice after further analysis[a]	Factors with strong and moderate level of evidence
To be further explored in clinical research[b]	Risk factors associated with rupture but with low level of evidence from a single high-quality study (in absence of other studies)
	Factors with inconsistent evidence if evidence was available from >3 low-quality studies and inconsistency was based on 1 low-quality study.

[a]To be suitable for use in clinical practice, these factors should first be tested in multivariate analysis and combined with the risk factors currently used in clinical practice in a prediction model.
[b]These association of these risk factors with rupture should first be further confirmed in larger high quality prospective cohort studies.

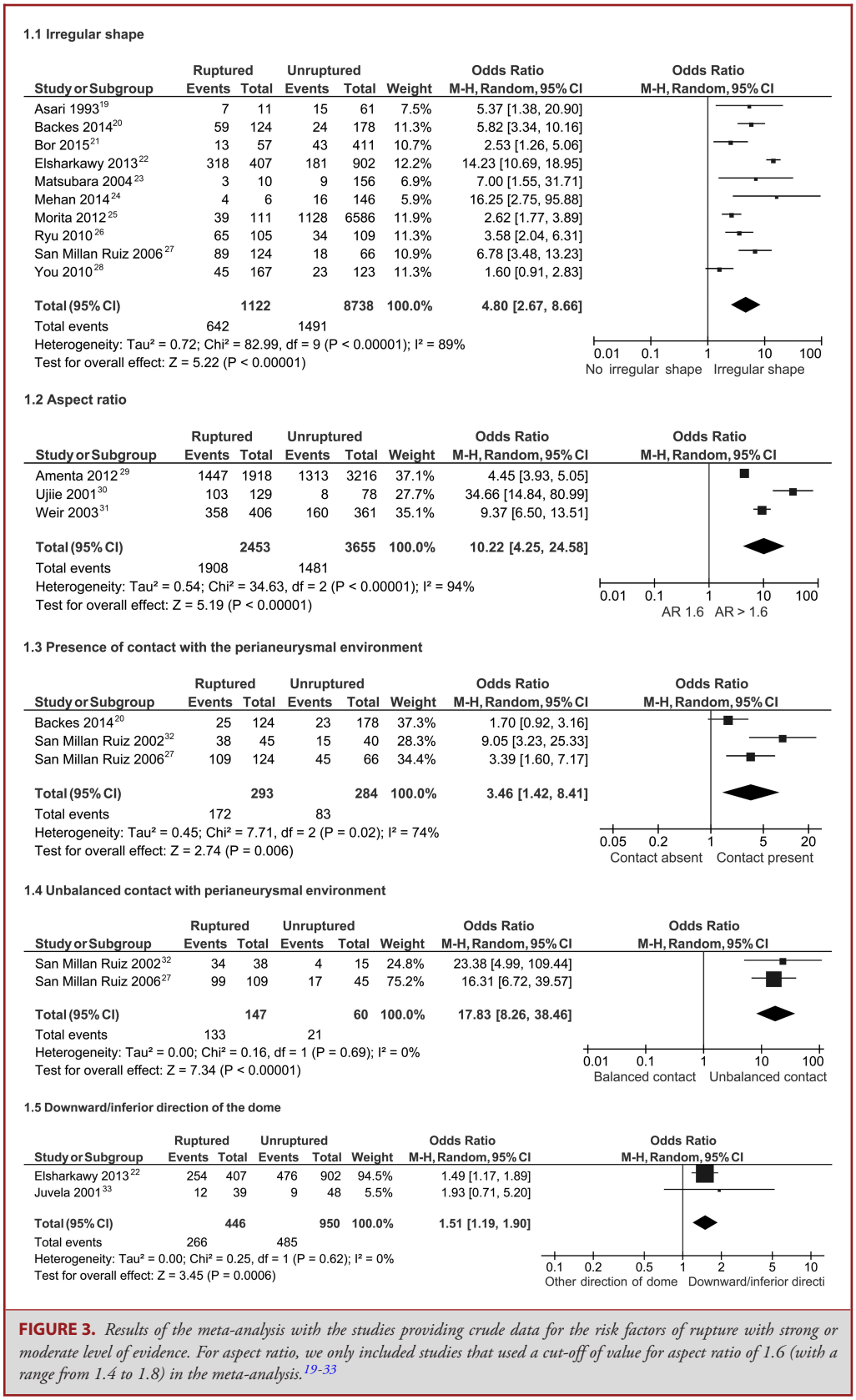

FIGURE 3. *Results of the meta-analysis with the studies providing crude data for the risk factors of rupture with strong or moderate level of evidence. For aspect ratio, we only included studies that used a cut-off of value for aspect ratio of 1.6 (with a range from 1.4 to 1.8) in the meta-analysis.*[19-33]

Low Level of Evidence

There were 61 factors associated with rupture with low level of evidence (**Table**, **Supplemental Digital Content 3**). Of these factors, 9 were genetic factors (including polymorphisms in the endothelial nitric oxide synthase gene, the complement factor H gene, the elastin gene, the Jun proto-oncogene, the synuclein alpha gene, the matrix metalloproteinase 1 and 9 genes, an interferon gene, and fibronectin 1 and 5'-aminolevulinate synthase 2 gene). Eight were molecular factors, including serum levels of several proteins. Twenty-two were morphological factors (including carotid intima-media thickness, intraluminal thrombus, different geometric indices, different configurations of the circle of Willis, and several variants of definitions of aneurysm shape), and 22 were hemodynamic factors (including several blood pressure effects on the common carotid artery, different characterizations of flow, and size of the impingement of flow on the wall).

Of the factors with low level of evidence, 16 genetic, morphological, and hemodynamic risk factors fulfilled our predefined criteria (as outlined in Table 2) to have potential for further confirmation in future large high-quality prospective cohort studies (underlined in the **Table**, **Supplemental Digital Content 3**), including the 27 VNTR and G894T single nucleotide polymorphisms of the endothelial nitric oxide synthase gene, intraluminal thrombus, nonsphericity index (deviation from spherical shape), undulation index, ellipticity index (variant of aspect ratio defined with 3D variables), spherical shape, pear shape, unilateral hypoplastic A1 segment, ordinary type circle of Willis, deviated neck orifice position, flow impingement size, inflow concentration index, straight flow into the aneurysm, the smallest angle in the bifurcation on which the aneurysm is present, complex flow pattern in the aneurysm, and unstable flow pattern in the aneurysm.

Factors Not Associated with Rupture

Factors not associated with rupture supported by strong or moderate evidence were not found (**Table**, **Supplemental Digital Content 4**). There were 56 nonassociated factors with low level of evidence. Of these 56 factors, 3 were genetic factors (including the polymorphisms in the genetic risk loci from the genome-wide association studies on intracranial aneurysms, and in the elastin and the endoglin gene) and 10 were molecular factors (including serum markers such as lipids, angiotensin II and renin activity, and elastase to alpha-1-antitrypsin ratio). There were 22 morphological factors (including calcification of the wall, different geometric indices, and several variants of definitions of aneurysm shape), and 21 were hemodynamic factors (including wall shear stress [WSS, the tangential force produced by blood moving across the vessel wall] in the parent artery and the ostium region, different characterizations of flow [including flow angles], and factors related to blood pressure).

Factors with Inconsistent Evidence

Eighteen factors had inconsistent evidence (**Table**, **Supplemental Digital Content 5**). There were 6 morphological factors with inconsistent evidence, including the diameter of the aneurysm neck, the diameter of the parent artery, lateral and posterior direction of the aneurysm dome, the mean curvature norm (a measure of the predominant shape characteristic of the aneurysm surface), and bulge location (the ratio between the height from the neck plane to the maximal longitudinal diameter parallel with the neck plane to the aneurysm height). We found 12 hemodynamic factors with inconsistent evidence, including aneurysm pulsation, several definitions of WSS, energy loss (the value of collision power from hemodynamic sources divided by the aneurysm volume), and different characterizations of flow.

Of the factors with inconsistent evidence, aneurysm pulsation and maximal WSS were factors defined as having potential for further confirmation in larger high-quality prospective cohort studies (underlined in the **Table**, **Supplemental Digital Content 5**).

DISCUSSION

In this review, we studied 144 different risk factors for rupture and found irregular aneurysm shape as a risk factor with potential for use in clinical practice. Aspect ratio, size ratio, bottleneck factor, height-to-width ratio, contact with the perianeurysmal environment, large volume-to-ostium ratio, and dome direction also have potential for use in clinical practice but should first be confirmed in well-powered studies using multivariable analysis and incorporated in prediction models. In addition, we intended to perform a formal meta-analysis, but the large heterogeneity across the studies, the lack of crude data in many studies, and the little consistency in the definitions of the risk factors under study significantly limited the amount of data suitable for such a meta-analysis. Therefore the results should be interpreted with caution.

Irregular shape of the aneurysm had the highest potential for use in clinical practice. The validity of the meta-analysis for this risk factor is hampered by the heterogeneity across the studies assessing irregular shape. Furthermore, the availability of crude data in the studies on irregular shape was limited, which led to inclusion of only 10 of 26 studies in the meta-analysis. Despite these limitations, we still recommend the use of this risk factor in clinical practice, because the evidence for this risk factor was based on 10 high-quality studies, of which 4 were prospective cohort studies, and the pooled OR was substantial and statistically highly significant.

The evidence for the risk factor aspect ratio was derived from 10 high-quality studies, of which only 1 had a prospective cohort design. For this factor, we found a large effect size with a pooled OR of 10.2 (95% CI 4.3-24.6). However, because we again found substantial heterogeneity across studies while the pooled OR was based on only 3 of the 10 studies due to a lack of

consistency in the use of a cut-off point in the different studies, this pooled OR should be interpreted with caution, and this risk factor is therefore not yet suitable for use in clinical practice. The evidence for the other 7 morphological factors was based on high-quality studies, of which none had a prospective cohort design. Furthermore, the meta-analysis of the factors presence of contact with the perianeurysmal environment, unbalanced nature of this contact, and downward/inferior direction of the dome was based on 3 or 2 studies, and, therefore, the pooled OR's of these factors should also be interpreted with caution. Most importantly, we should recognize that the 8 morphological factors associated with an increased risk of aneurysm rupture might be related to the size of the aneurysm, a well-established risk factor,[6,13] because they are calculated with size or variants of size (eg, height, width, and volume) as a variable. Therefore, the 8 morphological risk factors aspect ratio, size ratio, bottleneck factor, height-to-width ratio, presence of contact with the perianeurysmal environment, unbalanced nature of this contact, volume-to-ostium ratio, and a downward/inferior direction of the aneurysm dome should first be studied in a multivariate analysis and be incorporated in prediction models of rupture to assess their independence from size and from each other, and these models should be validated before implementation of these risk factors in clinical practice.

The previous systematic reviews and meta-analysis on risk factors for rupture[6,13] included only prospective cohort studies, of which the results could be directly incorporated in clinical practice and are incorporated in the current guidelines for treatment of unruptured aneurysms from the European Stroke Organization and the American Heart Association/American Stroke Association.[14,15] This review provides an overview of all the other risk factors (including genetic, molecular, morphological, and hemodynamic factors) that have potential for use in clinical practice. Another strong aspect of our current review is the restriction to studies with factors that can be measured with easily accessible diagnostic tools (such as computed tomography angiography or magnetic resonance angiography, or from peripheral blood samples) before the aneurysm is treated. Therefore, our review also provides an overview of all potential clinically relevant risk factors and can be used as a starting point for further search for clinically relevant risk factors for rupture. Another unique aspect of our review is the assessment of the methodological quality score of each of the studies and incorporation of this score in the assessment of the potential of each risk factor, leading to a transparent and extensive overview of the available evidence for each of the risk factors.

Limitations

Our study demonstrates overall poor quality of the currently available studies on genetic, molecular, morphological, and hemodynamic factors and their association with rupture of aneurysms. This poor quality led to the identification of only 1 risk factor that can be used in clinical practice and only a limited amount of risk factors with potential as a risk factor amongst a total of 144 risk factors identified, which is rather disappointing. However, the overview of the risk factors that do not have potential and should not be studied in future studies anymore also adds to the current literature. Another limitation of our study is that in our method a risk factor could only reach strong or moderate evidence if it was studied in 2 or more high-quality studies. This could have led to an overrepresentation of studies investigating factors that can be easily measured in clinical practice and therefore investigated by multiple authors, while risk factors that are not easy to measure are relatively less often studied and can therefore never reach a high level of evidence. We do not think this limits our results, because we aimed at identifying risk factors that are easy to measure in clinical practice and we also highlighted risk factors with limited level of evidence that have potential for further research. Also, we considered morphological risk factors assessed with either computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography as equal, while the quality of the measurement could have differed between these different imaging studies. At last, the risk factors identified were not evenly spread in number over the different categories we predefined (genetic, molecular, morphological, and hemodynamic factors), which can be the result of publication bias and might have led to an underestimation of potency of risk factors in 1 or more of these categories.

CONCLUSION

Irregular shape of the aneurysm should be added as a predictor of the risk of rupture to the predictors currently used in clinical practice. The morphological factors aspect ratio, size ratio, bottleneck factor, height-to-width ratio, volume-to-ostium ratio, presence of contact with the perianeurysmal environment, unbalanced nature of this contact, and a downward/inferior direction of the aneurysm dome should first be tested in multivariate analysis and confirmed in prediction models before use in clinical practice. Eighteen genetic, morphological, and hemodynamic risk factors for rupture were identified as potentially relevant for further clinical research.

Disclosures

Rachel Kleinloog was supported by a "Focus en Massa" cardiovascular research grant by the University Utrecht, the Netherlands. Ynte M. Ruigrok was supported by a clinical fellowship grant by the Netherlands Organization for Scientific Research (NOW; project no. 40-00703-98-13533). The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. *Lancet Neurol*. 2011;10(7):626-636.
2. Gabriel RA, Kim H, Sidney S, et al. Ten-year detection rate of brain arteriovenous malformations in a large, multiethnic, defined population. *Stroke*. 2010;41(1):21-26.

3. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. *Lancet*. 2007; 369(9558):306-318.
4. Nieuwkamp DJ, Setz LE, Algra A, Linn FH, de Rooij NK, Rinkel GJ. Changes in case fatality of aneurysmal subarachnoid haemorrhage over time, according to age, sex, and region: a meta-analysis. *Lancet Neurol*. 2009;8(7):635-642.
5. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ. Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. *J Neurol Neurosurg Psychiatry*. 2007;78(12):1365-1372.
6. Greving JP, Wermer MJ, Brown RD, Jr, et al. Development of the PHASES score for prediction of risk of rupture of intracranial aneurysms: a pooled analysis of six prospective cohort studies. *Lancet Neurol*. 2014;13(1):59-66.
7. Juvela S, Poussa K, Lehto H, Porras M. Natural history of unruptured intracranial aneurysms: a long-term follow-up study. *Stroke*. 2013;44(9):2414-2421.
8. Broderick JP, Brown RD, Jr, Sauerbeck L, et al. Greater rupture risk for familial as compared to sporadic unruptured intracranial aneurysms. *Stroke*. 2009;40(6):1952-1957.
9. de Rooij NK, Rinkel GJ, Dankbaar JW, Frijns CJ. Delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review of clinical, laboratory, and radiological predictors. *Stroke*. 2013;44(1):43-54.
10. Burns JD, Huston J 3rd, Layton KF, Piepgras DG, Brown RD, Jr. Intracranial aneurysm enlargement on serial magnetic resonance angiography: frequency and risk factors. *Stroke*. 2009;40(2):406-411.
11. Review Manager (RevMan) [Computer Program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, *The Cochrane Collaboration*, 2014.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
13. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. *Stroke*. 2007;38(4):1404-1410.
14. Steiner T, Juvela S, Unterberg A, Jung C, Forsting M, Rinkel G. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. *Cerebrovasc Dis*. 2013;35(2):93-112.
15. Thompson BG, Brown RD, Jr, Amin-Hanjani S, et al. Guidelines for the Management of Patients With Unruptured Intracranial Aneurysms: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke*. 2015;46(8):2368-2400.
16. Nakaoka H, Takahashi T, Akiyama K, et al. Differential effects of chromosome 9p21 variation on subphenotypes of intracranial aneurysm: site distribution. *Stroke*. 2010;41(8):1593-1598.
17. Bilguvar K, Yasuno K, Niemelä M, et al. Susceptibility loci for intracranial aneurysm in European and Japanese populations. *Nat Genet*. 2008;40(12):1472-1477.
18. Parlea L, Fahrig R, Holdsworth DW, Lownie SP. An analysis of the geometry of saccular intracranial aneurysms. *AJNR Am J Neuroradiol*. 1999;20(6):1079-1089.
19. Asari S, Ohmoto T. Natural history and risk factors of unruptured cerebral aneurysms. *Clin Neurol Neurosurg*. 1993;95(3):205-214.
20. Backes D, Vergouwen MDI, Velthuis BK, et al. Difference in aneurysm characteristics between ruptured and unruptured aneurysms in patients with multiple intracranial aneurysms. *Stroke*. 2014;45(5):1299-1303.
21. Bor ASE, Groenestege ATT, Terbrugge KG, et al. Clinical, radiological, and flow-related risk factors for growth of untreated, unruptured intracranial aneurysms. *Stroke*. 2015;46(1):42-48.
22. Elsharkawy A, Lehecka M, Niemela M, et al. Anatomic risk factors for middle cerebral artery aneurysm rupture: Computed tomography angiography study of 1009 consecutive patients. *Neurosurgery*. 2013;73(5):825-837.
23. Matsubara S, Hadeishi H, Suzuki A, Yasui N, Nishimura H. Incidence and risk factors for the growth of unruptured cerebral aneurysms: observation using serial computerized tomography angiography. *J Neurosurg*. 2004;101(6):908-914.
24. Mehan WA, Romero JM, Hirsch JA, et al. Unruptured intracranial aneurysms conservatively followed with serial CT angiography: Could morphology and growth predict rupture? *J Neurointervent Surg*. 2014;6(10):761-766.
25. UCAS Japan InvestigatorsMorita A, Kirino T, et al. The natural course of unruptured cerebral aneurysms in a Japanese cohort. *N Engl J Med*. 2012;366(26): 2474-2482.
26. Ryu CW, Kwon OK, Koh JS, Kim EJ. Analysis of aneurysm rupture in relation to the geometric indices: aspect ratio, volume, and volume-to-neck ratio. *Neuroradiology*. 2011;53(11):883-889.
27. San Millan Ruiz D, Yilmaz H, Dehdashti AR, Alimenti A, de Tribolet N, Rufenacht DA. The perianeurysmal environment: influence on saccular aneurysm shape and rupture. *AJNR Am J Neuroradiol*. 2006;27(3):504-512.
28. You SH, Kong DS, Kim JS, et al. Characteristic features of unruptured intracranial aneurysms: predictive risk factors for aneurysm rupture. *J Neurol Neurosurg Psychiatry*. 2010;81(5):479-484.
29. Amenta PS, Yadla S, Campbell PG, et al. Analysis of nonmodifiable risk factors for intracranial aneurysm rupture in a large, retrospective cohort. *Neurosurgery*. 2012;70(3):693-699.
30. Ujiie H, Tamano Y, Sasaki K, Hori T. Is the aspect ratio a reliable index for predicting the rupture of a saccular aneurysm? *Neurosurgery*. 2001;48(3):495-503.
31. Weir B, Amidei C, Kongable G, et al. The aspect ratio (dome/neck) of ruptured and unruptured aneurysms. *J Neurosurg*. 2003;99(3):447-451.
32. San Millan Ruiz D, Tokunaga K, Dehdashti AR, Sugiu K, Delavelle J, Rufenacht DA. Is the rupture of cerebral berry aneurysms influenced by the perianeurysmal environment? *Acta Neurochir Suppl*. 2002;82:31-34.
33. Juvela S, Poussa K, Porras M. Factors affecting formation and growth of intracranial aneurysms: a long-term follow-up study. *Stroke*. 2001;32(2):485-491.

Supplemental digital content *is available for this article at neurosurgery-online.com.*

COMMENTS

The authors perform a systematic review of aneurysm related risk factors for intracranial aneurysm rupture. They identify the following factors with a strong association: Irregular aneurysm shape, aspect ratio, size ratio, bottleneck factor, and height-to-width ratio. They identify the following factors with a moderate association: presence of contact with the perianeurysmal environment, unbalanced nature of this contact, volume-to-ostium ratio and direction of the aneurysm dome. The authors have clearly devoted a great deal of time and effort in researching and synthesizing this systematic review on a topic that is both inconsistent and heterogeneous and they should be congratulated on this publication.

Many previous systematic reviews have focused on aneurysm formation[1,2] and growth[3,4] rather than rupture itself. The last meta-analysis on the risk of rupture was published in 2007 and found that age >60 years, female gender, Japanese or Finnish descent, size >5 mm, posterior circulation location, and symptoms were all risk factors for rupture.[5] A retrospective review of over 2000 patients identified AR >1.6, dome diameter >10 mm, a deviated neck, and right-sidedness as independent risk factors for rupture.[6] The topic is a difficult one since many aneurysms are analyzed post-rupture when characteristics may have changed. All of these clinical and aneurysm risk factors should be kept in mind when deciding which unruptured aneurysms should be treated and which should be observed.

Justin Mascitelli
J. Mocco
New York, New York

1. Clarke M. Systematic review of reviews of risk factors for intracranial aneurysms. Neuroradiology. Aug 2008;50(8):653-664.
2. Vlak MH, Algra A, Brandenburg R, Rinkel GJ. Prevalence of unruptured intracranial aneurysms, with emphasis on sex, age, comorbidity, country, and time period: a systematic review and meta-analysis. Lancet Neurol. Jul 2011;10(7):626-636.

3. Brinjikji W, Zhu YQ, Lanzino G, et al. Risk Factors for Growth of Intracranial Aneurysms: A Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol. Apr 2016;37(4):615-620.
4. Backes D, Rinkel GJ, Laban KG, Algra A, Vergouwen MD. Patient- and Aneurysm-Specific Risk Factors for Intracranial Aneurysm Growth: A Systematic Review and Meta-Analysis. Stroke. Apr 2016;47(4):951-957.
5. Wermer MJ, van der Schaaf IC, Algra A, Rinkel GJ. Risk of rupture of unruptured intracranial aneurysms in relation to patient and aneurysm characteristics: an updated meta-analysis. Stroke. Apr 2007;38(4):1404-1410.
6. Amenta PS, Yadla S, Campbell PG, et al. Analysis of nonmodifiable risk factors for intracranial aneurysm rupture in a large, retrospective cohort. Neurosurgery. Mar 2012;70(3):693-699; discussion 699-701.

The authors have performed a valiant effort to report a systemic review of 102 articles, discussing 144 risk factors in present report.

The risk factors for rupture of aneurysm have been discussed widely in literature in last 50 years. Multiple different studies have emphasized the importance of genetic, molecular, morphological, and hemodynamic risk factors in different articles. However, discussion of all possible factors for the same population is lacking in the present literature.

The present article attempts to address this point. Though, the authors have done a commendable job. Several factors contributing to the rupture of the aneurysm were still missing, despite considering so many.Results of the role of morphological parameters predicting rupture of aneurysm are heterogeneous in literature.[1] As depicted several times, an inherent concern is that the results may be affected by the growth, or rupture itself.[2] They may vary for aneurysms in specific location,[3] and for multiple aneurysms.[4] Several inflammatory and genetic markers,[5] biomarkers[6] and hemodynamic factors[2] have been described in literature. Understandably, not all of them were considered in present report.

For analyzing few factors, only 3-4 studies were considered. Drawing conclusions from a small numbers of studies may lead to erroneous interpretation, if results of studies vary from each other. Higgins' method and calculation of I^2 are standard methods to comment on heterogeneity of the data,[7] which is followed in present study as well. However, the heterogeneous test results also become inconclusive when small numbers of studies are considered.

Despite the limitations of the pooled analysis as a statistical method, the factors discussed in this study may certainly act as starting point. We acknowledge their Herculean effort.

Tanmoy Maiti
Anil Nanda
Shreveport, Louisiana

1. Dhar S, Tremmel M, Mocco J, et al. Morphology parameters for intracranial aneurysm rupture risk assessment. Neurosurgery. 2008;63(2):185-196; discussion 196-187.
2. Can A, Du R. Association of Hemodynamic Factors With Intracranial Aneurysm Formation and Rupture: Systematic Review and Meta-analysis. Neurosurgery. 2016;78(4):510-520.
3. Lin N, Ho A, Charoenvimolphan N, Frerichs KU, Day AL, Du R. Analysis of morphological parameters to differentiate rupture status in anterior communicating artery aneurysms. PLoS One. 2013;8(11):e79635.
4. Jiang H, Weng YX, Zhu Y, Shen J, Pan JW, Zhan RY. Patient and aneurysm characteristics associated with rupture risk of multiple intracranial aneurysms in the anterior circulation system. Acta Neurochir (Wien). 2016;158(7):1367-1375.
5. Chalouhi N, Hoh BL, Hasan D. Review of cerebral aneurysm formation, growth, and rupture. Stroke. 2013;44(12):3613-3622.
6. Hussain S, Barbarite E, Chaudhry NS, et al. Search for Biomarkers of Intracranial Aneurysms: A Systematic Review. World Neurosurg. 2015;84(5):1473-1483.
7. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-560.

The authors have performed a systematic review of the literature in an attempt to identify risk factors for aneurysm rupture that might be useful in clinical practice. They analyzed 102 studies and 144 different risk factors. They identified strong evidence to support the following morphological factors as risk factors for aneurysm rupture: irregular shape of the aneurysm (multilobulated or presence of blebs), larger aspect ratio (aneurysm height / neck diameter), larger size ratio (aneurysm height/average parent vessel diameter), larger bottleneck factor (aneurysm width/neck diameter), and larger aneurysm height to aneurysm width ratio. For irregular shape and aspect ratio, the authors were able to calculate a pooled odds ratio of 4.8 and 10.2 (95% confidence interval), respectively, for aneurysm rupture. The authors conclude that irregular shape is a morphological risk factor for aneurysm rupture that should be used in clinical practice because the pooled odds ratio is based on 10 high quality studies, of which 4 were prospective cohort studies.

Frances Murphey described the Murphey's teat many years ago – referring to the rupture point (irregularity) on an aneurysm that can sometimes be observed following subarachnoid hemorrhage. The notion that aneurysm irregularity corresponds with a higher risk of rupture intuitively makes sense and is consistent with what we already know about cerebral aneurysms. The authors point out that their ability to perform pooled statistical analysis was limited by significant heterogeneity among studies. They also point out that many of the risk factors for rupture that they identified are a function of aneurysm size, which could be a major confounder in this analysis. We agree that future study is needed in a prospective fashion to draw firm conclusions about these proposed risk factors. This study serves as a good starting point and helps to frame future conversations regarding morphologic risk factors for aneurysm rupture.

M. Neil Woodall
Robert F. Spetzler
Phoenix, Arizona