ARTICLE

Bleeding risk of small intracranial aneurysms in a population treated in a reference center

Risco de sangramento de aneurismas intracranianos pequenos em uma população tratada em um centro de referência

Guilherme LEPSKI[1], Carlos A. F. LOBÃO[1], Stella TAYLOR[1], Paulo M. MESQUITA FILHO[1], Marcos TATAGIBA[1]

ABSTRACT

Large multicenter studies have shown that small intracranial aneurysms are associated with a minimal risk of bleeding. Nevertheless, other large series have shown that most ruptured aneurysms are, in fact, the smaller ones. In the present study, we questioned whether small aneurysms are indeed not dangerous. **Methods:** We enrolled 290 patients with newly-diagnosed aneurysms at our institution over a six-year period (43.7% ruptured). We performed multivariate analyses addressing epidemiological issues, cardiovascular diseases, and three angiographic parameters (largest aneurysm diameter, neck diameter and diameter of the nutrition vessel). Risk estimates were calculated using a logistic regression model. Aneurysm size parameters were stratified according to receiver operating characteristic (ROC) curves. Finally, we calculated odds ratios for rupture based on the ROC analysis. **Results:** The mean largest diameter for the ruptured versus unruptured groups was 13.3 ± 1.7 mm versus 22.2 ± 2.2 mm ($p < 0.001$). Multivariate analysis revealed a positive correlation between rupture and arterial hypertension ($p < 0.001$) and an inverse correlation with all three angiographic measurements (all $p < 0.01$). Aneurysms from the anterior cerebral artery bled more often ($p < 0.05$). According to the ROC curves, at the largest diameter of 15 mm, the sensitivity and specificity to predict rupture were 83% and 36%, respectively. Based on this stratification, we calculated the chance of rupture for aneurysms smaller than 15 mm as 46%, which dropped to 25% for larger aneurysms. **Conclusion:** In the population studied at our institution, small aneurysms were more prone to bleeding. Therefore, the need for intervention for small aneurysms should not be overlooked.

Keywords: Intracranial aneurysm, rupture.

RESUMO

Grandes estudos multicêntricos demostram que aneurismas intracranianos pequenos são associados a risco de sangramento mínimo. Outras grandes séries têm evidenciado que aneurismas rotos são em sua maioria os pequenos. Neste estudo questionamos até que ponto os aneurismas pequenos não são perigosos. **Métodos:** Avaliamos 290 novos casos de aneurismas tratados em nossa instituição durante 6 anos (43,7% rotos). Realizamos análises multivariadas com aspectos epidemiológicos dos pacientes, doenças cardiovasculares e três parâmetros angiográficos: maior diâmetro, diâmetro do colo e diâmetro do vaso nutridor do aneurisma. Estimativas de risco foram calculadas utilizando-se modelo de regressão logística. Parâmetros do tamanho aneurismático foram estratificados de acordo com curvas ROC. Também calculamos a razão de chances (*odds ratios*) de ruptura baseadas nas análises das curvas ROC. **Resultados:** O maior diâmetro médio para os grupos de aneurismas rotos e não-rotos foi 13.3 ± 1.7mm e 22.2 ± 2.2 ($p < 0.001$). Análises multivariadas revelaram uma correlação positiva entre ruptura aneurismática e hipertensão arterial ($p < 0.001$) e uma correlação inversa entre ruptura e as três medidas angiográficas ($p < 0.01$). Aneurismas da artéria cerebral anterior foram os que mais sangraram ($p < 0.05$). Análises das curvas ROC demonstram que no maior diâmetro de 15mm, a sensibilidade e especificidade para se predizer ruptura são de 83% e 36%. Baseando-se nessas estratificações, calculamos uma chance de ruptura para aneurismas menores de 15mm de 46% e de 25% para aneurismas maiores. **Conclusão:** Na população estudada, aneurismas pequenos são mais propensos a romper. Desta forma, a necessidade de intervenção para aneurismas pequenos não deve ser relevada.

Palavras-chave: Aneurisma intracraniano, ruptura.

Large multicenter studies on unruptured aneurysms have shown a relatively low rupture rate for smaller aneurysms compared with larger ones[1,2]. Nevertheless, controversy on the subject still persists, based on the fact that a high percentage of patients admitted to reference centers with subarachnoidal hemorrhage (SAH) present with aneurysms smaller

[1]Universitätsklinik für Neurochirurgie, Eberhard Karls University, Tübingen, Deutschland.

Guilherme Lepski (iD) https://orcid.org/0000-0002-9030-4192; Carlos Augusto Ferreira Lobão (iD) https://orcid.org/0000-0001-7789-1663; Paulo M. Mesquita Filho (iD) https://orcid.org/0000-0003-1375-9203; Stella Taylor (iD) https://orcid.org/0000-0001-7186-8868; Marcos Tatagiba (iD) https://orcid.org/0000-0002-1627-9937

Correspondence: Carlos A. F. Lobão; Eberherd-Karls University - Neurosurgery Hoppe-Seyler-Str. 4 Tuebingen 72072, Germany; E-mail: caflobao@yahoo.com.br

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than 5 mm[3,4,5,6,7,8]. The prevalence of intracranial aneurysms varies from 3.7% in prospective autopsy studies to 6.0% in prospective angiographic studies[9]. Moreover, they lead to a relatively high rate of morbidity-mortality, with a rate of SAH of about 1.4% per year[10], which is in turn associated with a mortality rate of up to 50%[11]; furthermore, half the survivors sustain irreversible brain damage[12]. Known predictors for rupture include age, hypertension, history of SAH, aneurysm size and geographic location. Certain populations, like the Finns and Japanese, have considerably higher risks of rupture (3.6-fold and 2.8-fold, respectively)[10] than other populations, and some genetic predispositions, such as polymorphisms on the SOX17 transcriptor regulation gene, endothelin receptor A gene, or cyclin-dependent kinase inhibitor genes, have been recently implicated in aneurysm formation[13].

To date, the best evidence for risk of SAH from unruptured intracranial aneurysms is derived from the International Study of Unruptured Intracranial Aneurysms (ISUIA)[14]. Based on this and other studies[2,5,9,15], the current recommendation is that asymptomatic patients harboring aneurysms smaller than 7 mm in diameter, without a previous history of rupture, should not receive treatment[16,17]. By contrast, other studies have suggested that aneurysms from the anterior communicating complex (ACoA), as well as those with large maximal diameter/neck diameter ratios, are more prone to bleed and must, therefore, be treated differently than that recommended by the guidelines[18,19,20]. Additionally, many retrospective series from large reference centers have reported a high proportion of small aneurysms among patients admitted with SAH[3,21,22,23,24]. More specifically, up to 88% of patients with SAH had aneurysms smaller than 10 mm in diameter at the time of the original diagnosis[23]. These data support the idea that the risk of bleeding associated with small aneurysms should not be underestimated. Several authors have tried to explain the discrepancy between the ISUIA results and large single-center experiences. We suggest an important variable in this discrepancy may be selection bias.

In the present study, we questioned the premise that small aneurysms do not carry a risk of rupture at the time of diagnosis. To this end, we retrospectively evaluated 290 patients referred to the University of Tübingen (Germany) over a six-year period. We propose a new method to address the relationship between aneurysm size and prevalence of rupture, based on logistic regression. Aneurysms were classified by size (small and large) based on the receiver operating characteristic (ROC) curve stratification instead of by arbitrarily defining size thresholds.

METHODS

For this study, we obtained clinical and radiological information for all patients diagnosed with intracranial aneurysms at the University of Tübingen, which included patient age, sex, tobacco dependence, comorbidities (e.g., diabetes mellitus, arterial hypertension or other vascular diseases), and location of aneurysm. Patients were excluded from the study if they had non-aneurysmal SAH. When patients had multiple aneurysms, ruptured intracranial aneurysms were identified by angiographic determinants or by direct observation during surgery.

Digital subtraction angiography and three-dimensional computed tomography angiography were used to evaluate the morphology of intracranial aneurysms. The following measurements were independently performed by two experienced neurosurgeons (C.A.F.L. and S.T.): 1) largest aneurysm diameter; 2) neck diameter; and 3) diameter of the nutrition vessel (Figure 1). Agreement between the two observers was quantified with the κ test. For further calculations, we used the mean values from both observers.

Continuous data were expressed as means ± standard errors. To assess data distribution, we applied the Shapiro-Wilk W test. Since all measured diameters obeyed normal distribution, mean comparisons were performed with Student's t-tests. To identify the independent parameters that had significant correlations with rupture, a multivariate logistic regression analysis was performed for all aneurysms (this is shown in a clustered color map). Categorical data were compared using a contingency analysis and Pearson's chi-square test. These data are shown graphically in mosaic plots. To address the relationship between size measurements and rupture at the time of diagnosis, we applied a logistic regression model and calculated the logistic probability of rupture. The resulting curve fit the model, and we present the curve, equation and curve coefficients. Additionally, we performed a ROC analysis to determine the optimal threshold value for each of the three measurements recorded (the area under the curve [AUC] reflects the goodness of the predictor). Based on this analysis, we calculated the sensitivity and specificity of the measures at the threshold. Finally, data were categorized into two groups (large and small values) according to the ROC analysis. We then compared the prevalence of rupture and other clinical features between groups.

For statistic computation and graphic representations, we used the JMP 11.1.1 software (SAS Institute Inc., NC, USA).

RESULTS

Series characterization

From January 2006 to December 2011, we collected clinical and radiological data from 290 consecutive and newly-diagnosed patients harboring intracranial aneurysms (346 aneurysms); 69% were female and 31% were male, with a mean age of 53.9 ± 14.4 years. Of the aneurysms, 43.7% were ruptured and 56.3% were unruptured. During this period, 30% of the patients were treated with endovascular procedures,
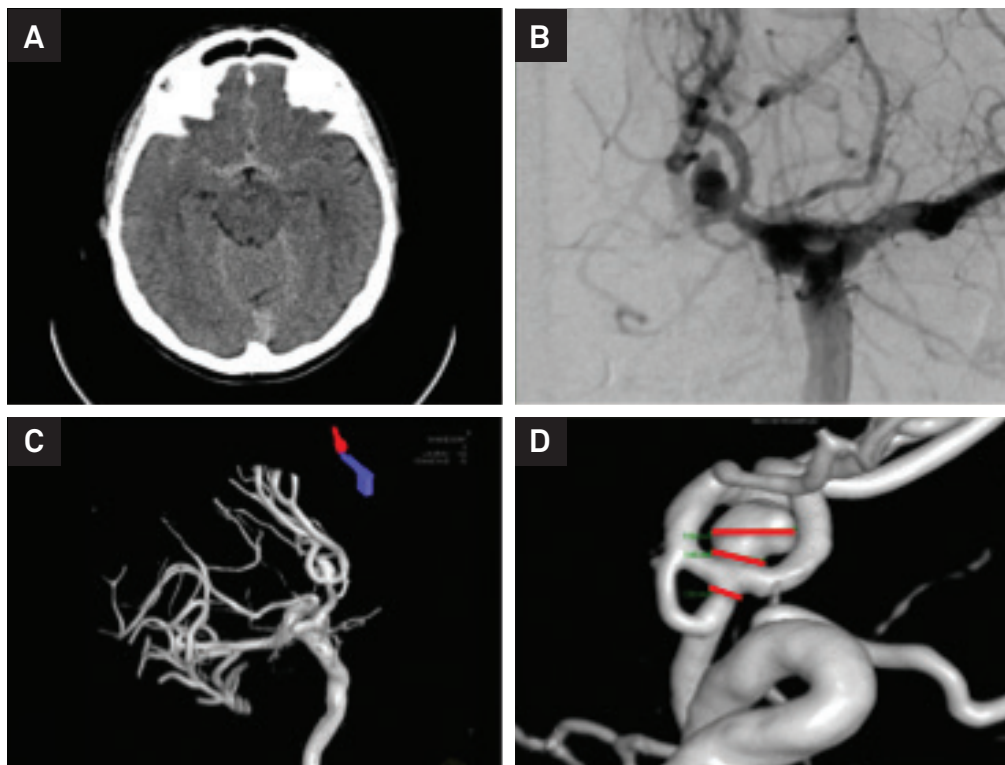
Figure 1. Illustrative case of a 42-year-old male patient who was admitted to our center on day 0 of a subarachnoid hemorrhage. A: CT-scan showing a Fisher 4 SAB grade with diffuse blood around the basal cisterns. B: digital subtraction angiography performed in emergency care, revealing a 6 mm anterior communicating complex aneurysm filled from the left internal carotid artery. C: three-dimensional reconstruction of the angio-CT scans. D: example of the measurements performed of the maximal aneurysm diameter, neck diameter, and diameter of the nutrition vessel.

while 70% were treated surgically. Arterial hypertension was the most frequent comorbidity encountered (26.3%), and tobacco dependence the second (6.2%). Forty-two patients out of 290 presented with more than one aneurysm. The most frequent localization was the middle cerebral artery (35.7%), followed by anterior cerebral artery/anterior communicating artery complex (ACA/ACoA, [33.4%]), then the internal carotid artery (including the communicating posterior segment, 18.3%), and finally, the vertebrobasilar system (11.1%). In total, 21.8% of the aneurysms in this series measured less than 5 mm in maximal diameter, 23.4% measured between 5–7 mm, 14.7% between 7–10 mm, and 34.4% were larger than 10 mm.

Clinical factors associated with rupture

The multivariate analysis (Figure 2A) revealed a positive correlation between arterial hypertension and rupture (Pearson's r = 0.2276, p < 0.001), tobacco dependence and hypertension (r = 0.1576, p < 0.01), other cardiovascular diseases and hypertension (r = 0.2061, p < 0.001), age and arterial hypertension (r = 0.2824, p < 0.001). We also show in Figure 2B and Figure 2C a contingency analysis for aneurysm localization and arterial hypertension versus chance of rupture. Aneurysms of the anterior cerebral artery and patients with arterial hypertension were at higher risk of bleeding (p < 0.05 and < 0.001, respectively).

In the ruptured group, 42.6% of aneurysms occurred in the ACA/ACoA, 16.3% in the internal carotid artery, 31.8% in the middle cerebral artery, and 9.3% in the vertebrobasilar system. In the unruptured group, these rates were 27.3% in the ACA/ACoA, 22.7% in the internal carotid artery, 36.9% in the middle cerebral artery, and 13.1% in the vertebrobasilar system. Therefore, there was a higher proportion of ACA/ACoA aneurysms in the ruptured group (p < 0.05, Pearson's chi-square).

Pairwise analysis revealed that the chance of rupture at the time of the original diagnosis was significantly higher for patients with a previous diagnosis of hypertension (Pearson's chi-square p < 0.001) and for aneurysms located in the ACA/ACoA complex (Pearson's chi-square p < 0.05). In the present series, we did not observe any relationship between rupture and diabetes mellitus, tobacco dependence, age, sex, or cardiovascular diseases other than hypertension.

Angiographic size measurements and rupture

All three angiographic parameters analyzed were inversely correlated with rupture, and strongly correlated with each other (largest diameter, r = -0.1576, p < 0.001, neck diameter, r = -0.1775, p < 0.001, and diameter of the nutrition vessel, r = -0.1725, p < 0.001; Figure 2A). Moreover, all measurements were strongly associated with each other (largest x neck: r = 0.8375, largest x nutrition: r = 0.8113, neck x nutrition: r = 0.7747; all p < 0.001).
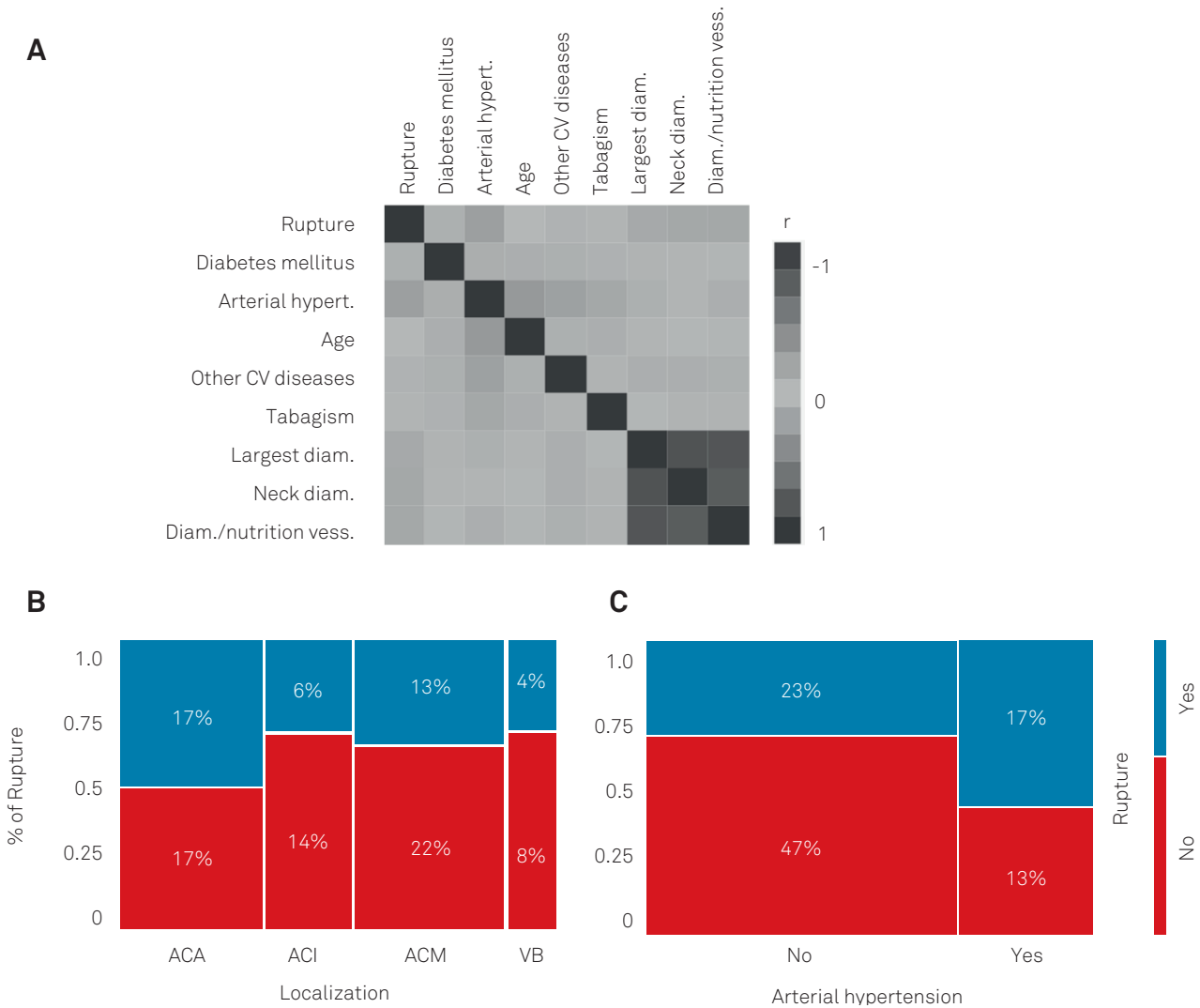
Figure 2. A: mosaic plot of the multivariate analysis, with Pearson's correlation coefficients represented in a colored map (scale on the right). Note that rupture (first line) is positively correlated with arterial hypertension (r = 0.2276, p < 0.001) but negatively correlated with the largest aneurysm diameter (r = -0.1576, p < 0.001), neck diameter (r = -0.1775, p < 0.001) and diameter of the nutrition vessel (r = -0.1725, p < 0.001). Moreover, all diameters measured have a strong direct linear relationship among each other (largest x neck: r = 0.8375, largest x nutrition: r = 0.8113, and neck x nutrition: r = 0.7747; all p < 0.001). In B and C, contingency analysis with mosaic plots for aneurysm localization versus chance of rupture (B), and arterial hypertension versus chance of rupture (C).

Rupture at the time of diagnosis, according to the logistic regression model

To evaluate the influence of each angiographic size parameter on the chance of rupture at the time of the original diagnosis, we applied logistic regression. According to our model, the chance of rupture (r = 1) obeys the following equation (1):

$$_{pLD}(r = 1) = 1 - (1 / 1 + e^{(-0.1628 - 0.0154 * LD)}) \quad (1)$$

Where p_{LD} refers to the chance of rupture as a function of the largest aneurysm diameter (LD is the largest diameter). The curve coefficients were -0.1628 ± 0.1431 and 0.0154 ± 0.0057 (whole model test, p < 0.05). As can be seen in Figure 3B, the bigger the largest diameter, the greater the chance of rupture at the time of diagnosis.

Similarly, we also found a negative association between aneurysm neck diameter and chance of rupture.

Accordingly, the chance of rupture is described by the following equation (2):

$$_{pND}(r = 1) = 1 - (1 / 1 + e^{(-0.1082 - 0.0354 * ND)}) \quad (2)$$

Where p_{ND} refers to the chance of rupture as a function of the aneurysm neck diameter (ND is the neck diameter). The curve coefficients were -0.1082 ± 0.1501 and 0.0354 ± 0.0121 (whole model test, p < 0.001) (Figure 3D).

Finally, we also examined the chance of rupture as a function of the diameter of the nutrition vessel, which yielded the following equation (3):

$$_{pDNV}(r = 1) = 1 - (1 / 1 + e^{(-01329 - 0.0480 * DNV)}) \quad (3)$$

Where p_{DNV} refers to the chance of rupture as a function of the diameter of the nutrition vessel (DNV is the diameter of the nutrition vessel). The curve coefficients were -0.1329 ± 0.1460 and 0.0480 ± 0.0160 (whole model test, p < 0.01) (Figure 3F).
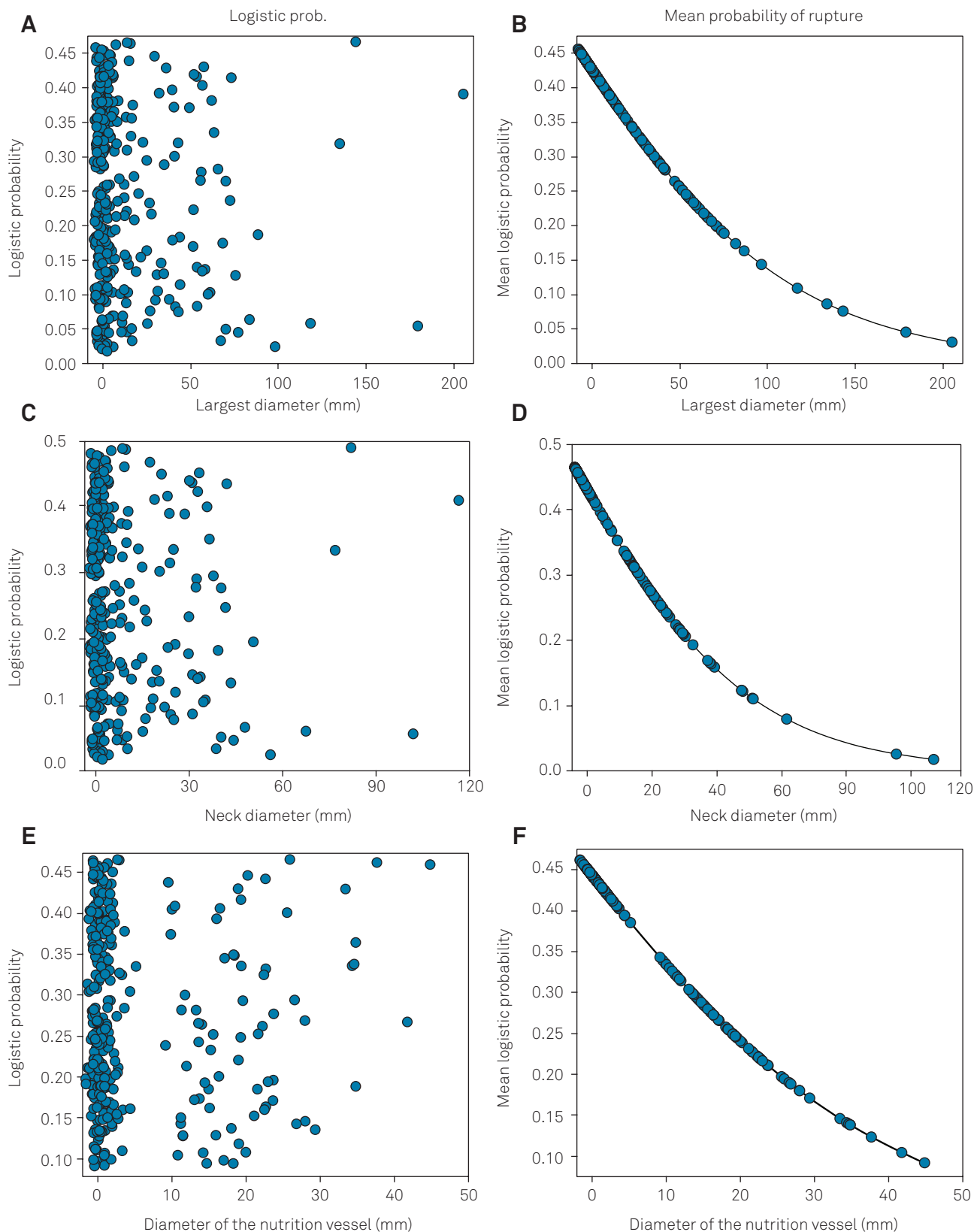
Figure 3. Logistic regression model used to predict chance of bleeding by the time of admission. On the left side, logistic probability plots of the largest aneurysm diameter (A), neck diameter (C), and diameter of the nutrition vessel (E). Each plot represents one patient. On the right side (B,D,F), mean logistic probability as a function of diameter, calculated based on the graphs on the left. The curve fittings indicate a logarithmic decay of the probability of bleeding as a function of diameter. For the largest aneurysm diameter (LD), the probability of rupture (r=1) was described by the equation pLD (r=1)= 1- (1/(1+e^((-0.1628-0.0154*LD)))). Similarly, for neck diameter, the deduced equation was pND (r=1)= 1- (1/(1+e^((-0.1082-0.0354*ND))), and for diameter of the nutrition vessel, pDNV (r=1)= 1-(1/(1+e^((- 0.1329-0.0480*DNV)))). All curves indicate that the larger the aneurysm, the higher the probability of rupture at the time of admission.

On the left side of Figure 3 we demonstrate logistic probability plots of the largest aneurysm diameter (Figure 3A), neck diameter (Figure 3C), and diameter of the nutrition vessel (Figure 3E).

Sample stratification according to size

In order to address the chance of rupture in the study population, we stratified the sample into two groups: large and small diameter aneurysms. Differently from what has previously been published, the threshold value used for this measurement was based on the ROC analysis using rupture as the outcome variable (Figure 4). First, the AUCs show how well the variables predict rupture. For large diameter, the AUC was 0.5812, for neck diameter, AUC = 0.6150, and for diameter of the nutrition vessel, AUC = 0.5881. Since all values were less than 0.7, we concluded that size was not a good predictor of bleeding in this population. The threshold value for the largest diameter was 14.97 mm; at this value, the sensitivity to predict rupture was 82.95% and the specificity was 35.53%. For the neck diameter, the threshold was
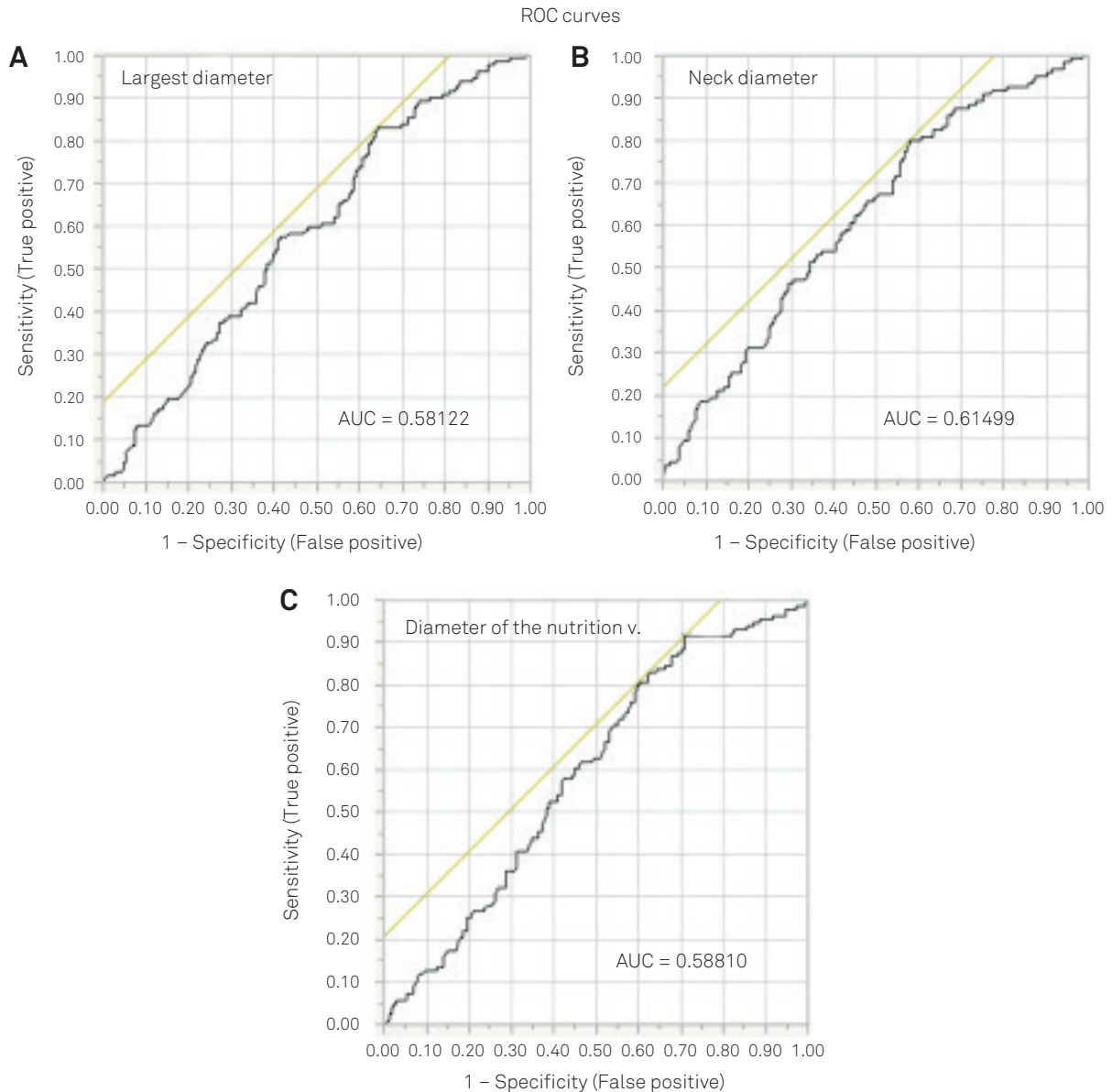

Figure 4. Receiver operating characteristic (ROC) analysis for largest diameter (A), neck diameter (B) and diameter of the nutrition vessel (C). The area under the curve indicates how well the variable predicts rupture. Since all values were lower than 0.7, we deduced that aneurysm size was, in fact, not a strong predictor of rupture. From the ROC tables, we calculated the values of the three diameter variables that were associated with the highest sensitivity and specificity. For the variable "largest diameter", the cut-off point was 14.97 mm; at this value, we found a sensitivity of 82.95% and specificity of 35.53% for rupture prediction. Similarly, the cut-off value for the neck diameter was 4.72 mm, with a sensitivity of 79.83% and a specificity of 41.9%. Finally, for the diameter of the nutrition vessel, the cut-off was 12.04 mm, which was associated with a sensitivity of 91.41% and specificity of 28.93%. The ROC analysis allows a more precise definition of representative groups within the sample population.
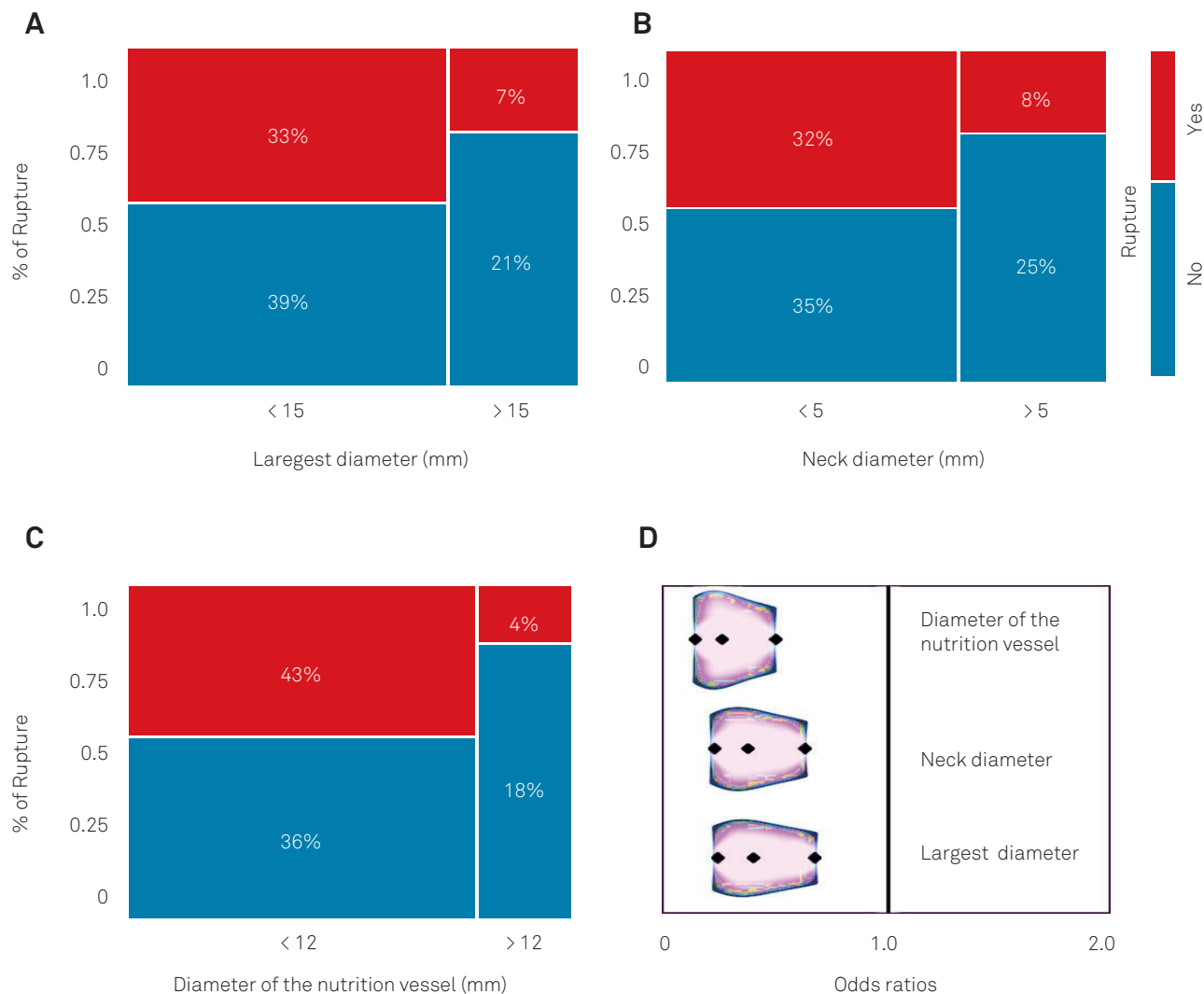
Figure 5. Contingency analysis for probability of rupture in two groups of patients (small and large aneurysms), which were defined based on the ROC analysis (Figure 4). In A, note a higher probability of rupture at the time of admission for patients harboring small aneurysms (large diameter less than 15 mm). For small aneurysms, the probability of rupture was 45.5%, which dropped to 24.7% if the aneurysm was larger than 15 mm in its maximal diameter (Pearson's chi-square p < 0.001). In B, a similar analysis was conducted for neck diameter; here, the probability of rupture was 47.5% for narrower necks (< 5mm) and 25.0% for wider necks (Pearson's chi-square p < 0.001). Finally, in C (nutrition vessel), the smaller nutrition (< 12 mm) was associated with 45.3% probability of rupture at the time of admission, which was much higher than the probability of 17.4% observed for patients with larger nutrition vessels (Pearson's chi-square p < 0.001). Next, we calculated the odds ratio for rupture in relation to each of the measurements. For largest diameter, OR = 0.3937 (95% CI = 0.2301 to 0.6735), for neck diameter, OR = 0.3688 (95% CI = 0.2167 to 0.6276), and for diameter of the nutrition vessel, OR = 0.2541 (95% CI = 0.1301 to 0.4962). Odds ratios below 1 indicate that, in our series, large sizes were in fact protective against rupture.

4.72 mm, with a sensitivity of 79.83% and a specificity of 41.90%. Finally, for the diameter of the nutrition vessel, the threshold was 12.04 mm, with a sensitivity of 91.41% and a specificity of 28.93%.

Based on this analysis, we divided the sample into aneurysms with largest diameter > and ≤ 15 mm, neck diameter > and ≤ 5 mm, and diameter of the nutrition vessel > and ≤ 12 mm (Figure 5). We observed that the chance of rupture at the time of diagnosis was 45.5% if the aneurysm was larger than 15 mm at its largest diameter and only 24.7% if it was less than or equal to 15 mm (p < 0.001, odds ratio [OR] = 0.3937, 95%CI = 0.2301 to 0.6735). Similarly, the chance

was 47.5% for aneurysms with necks smaller than 5 mm and 25.0% if the neck was larger than 5 mm (p < 0.001, OR = 0.3688, 95%CI = 0.2167 to 0.6276), and 45.3% for aneurysms whose nutrition vessel was smaller than 12 mm and only 17.4% for aneurysms whose nutrition vessel was larger than 12 mm (p < 0.001, OR = 0.2541, 95%CI = 0.1301 to 0.4962).

DISCUSSION

The prevalence of intracranial aneurysms is relatively high (2–6%, depending on the diagnostic method used)[9].

Furthermore, SAH is a potentially fatal condition, with a reported mortality rate of 52%[16] to 83%[15].

The retrospective arm of the ISUIA reported that the risk of rupture of an aneurysm smaller than 10 mm in a patient with no previous SAH was only 0.05%. Compared with other studies[6,15], the reported risk of rupture was 10 to 12 times lower than previously estimated. Based on this, the recommendation was to manage aneurysms measuring less than 10 mm expectantly. Later, detailed analyses of that study suggested that it may have suffered from methodological issues, such as selection bias[25].

In the ISUIA Part 2[2], higher rupture rates for small aneurysms were reported. Nevertheless, the major concerns regarding selection criteria remain. The annual rupture rates for aneurysms 7 mm to 12 mm in size were 0.5% in the anterior circulation and 2.9% in the posterior circulation. It is important to note that, in that study, aneurysms arising from the posterior communicating segment of the carotid were grouped under "posterior circulation". This might have contributed to the increased rupture risk in this group.

Based on the above report, mathematical algorithms have been developed to help the decision-making process regarding treatment necessity[26,27,28]. According to Mitchell and Jakubowski[26], intervention in patients with aneurysms smaller than 10 mm with no SAH was not justified (assumption based on lost life-years in the risk calculation). These authors concluded that intervention in unruptured aneurysms was justified only for patients up to 50 years of age (see also Vindlacheruvu et al.[27]). According to Yoshimoto[28], mathematical risk models suggest that prophylactic treatment of unruptured aneurysms may produce some benefit for large aneurysms. Moreover, given the low treatment-related morbidity-mortality in young populations harboring small aneurysms, intervention might be justified in this group[28].

Further analysis of the available data on unruptured aneurysms culminated with the following recommendations made by the Stroke Council of the American Heart Association[16]: 1) Asymptomatic intracavernous aneurysms should not be treated. In large symptomatic ones, the treatment should be individualized. 2) All symptomatic intradural aneurysms should be treated. 3) Incidental aneurysms with a diameter less than 10 mm should not be treated. Nevertheless, lesions approaching 10 mm, those with daughter aneurysm formation, those in young patients or in individuals with a family history of SAH, deserve special consideration for treatment. 4) Aneurysms found in association with a ruptured lesion and those with a diameter greater than 10 mm deserve strong consideration for treatment, especially in young patients.

The fact that rupture occurs preferentially in small aneurysms has been reported by numerous authors[5,6,21,22,23,24,29]. In the United States, it was reported that 80% of the 28,000 aneurysmal SAHs occurred in lesions smaller than 10 mm, indicating a 0.72% to 1.36% annual rupture rate for this group[30]. Inagawa[20] reported 24% rupture in aneurysms smaller than 5 mm, 48% for aneurysms measuring between 5 mm and 10 mm, and only 28% for those larger than 10 mm from a sample of 285 patients studied. Lai et al.[31] observed even more drastic numbers: according to their experience, SAH originating from aneurysms smaller than 5 mm occurred in 68% of patients (n = 267). Joo et al.[22] observed that 71.8% of their 627 cases of ruptured aneurysms presented with lesions smaller than 7 mm in diameter, and 87.9% were smaller than 10 mm. The high mortality rate in cases of rupture[8] highlights the importance of carefully deciding whether to treat patients harboring small aneurysms.

To explain the discrepancy between the reported reduced risk of rupture in small aneurysms and the higher prevalence of small aneurysms among those that rupture, one hypothesis suggests that aneurysms shrink after bleeding[21]. However, this hypothesis is not widely accepted, and some authors believe that aneurysms may even grow before rupturing[32,33]. Another hypothesis is that there seems to be a high-risk period soon after aneurysm formation, which is followed by a period of risk stabilization[26].

Although these phenomena may partially explain the controversy, we cannot ignore the possibility that methodological issues may have played an important role in the results reported in the ISUIA studies[34,35]. Selection bias has been pointed out as a major drawback in the ISUIA studies, with preferential treatment and exclusion of patients who were symptomatic, or who had aneurysms with certain morphological characteristics (e.g., daughter sacs or irregular borders), and those with a family history of SAH[1,4,5,8].

The study by Juvela et al.[5], though observational, provides first line evidence about the natural history of unruptured intracranial aneurysms. Aneurysm size and patient age were significant predictors of aneurysmal SAH, as was active cigarette smoking (all p < 0.05). Rinkel et al.[9] published a meta-analysis about the natural history of unruptured intracranial aneurysms. Among nine studies including a total of 3,907 patients, the overall risk of rupture was 1.9% per year (0.7% for unruptured aneurysms < 10 mm and 4% for intact lesions > 10 mm). According to Dickey et al.[36], the fact that the ISUIA and other studies mostly involved investigators from busy neurovascular centers, who routinely treated patients with larger aneurysms, created the false impression that the smaller aneurysms in their practice had a lower rupture rate[36].

Because rupture risk reflects a biological problem, it is unlikely that risk distribution changes abruptly beyond a certain threshold of aneurysm size. Supporting this idea, Dickey and Kailasnath[36] reported the "diameter-cube hypothesis," a mathematical model that describes the rupture potential of any given aneurysm as continuously increasing on the basis of the maximum diameter of the aneurysm cubed. Here, we propose a different way to calculate risk in a sample population, based on logistic regression. Our model predicts that

risk decreases logarithmically as a function of size. The low p values observed for the whole model-test support its robustness. Moreover, it has been proposed that the diameter of the nutrition vessel, or the neck diameter, either individually or in relation to the maximal diameter (size ratio), represent more reliable predictors of rupture[18,19,33].

Additionally, the ROC analysis revealed that these measurements have similar predictive power for ruptures (see AUCs). However, none of the parameters proved to be strong predictors in the present sample (AUC < 0.7). Notably, size stratification in this study was performed according to the ROC analysis, and large aneurysms with a reduced risk of bleeding (such as intracavernous, or those with calcified walls) were not excluded from the analysis. Exclusion would have generated higher risk values for large aneurysms but would have created selection bias, rendering the risk calculation inexact.

In conclusion, we have presented a mathematical model to describe the chance of aneurysm rupture at the time of diagnosis, based on logarithmic regression. Our model predicts a logarithmic decay of the chance of rupture as a function of aneurysm diameter. Size stratification according to the ROC analysis revealed that, at least for the population referred to our center in southern Germany, small aneurysms are especially worrisome. It remains to be determined whether this statement is also applicable to other populations.

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