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Rupture risk assessment for cerebral arteriovenous malformations

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Background. Hemorrhage from cerebral arteriovenous malformation (cAVM) is a formidable manifestation of the disease, which is characterized by a high risk of death and disability. Individual assessment of the hemorrhage risk from cAVM would allow choosing the most adequate treatment tactics taking into account the expected rupture risk and the patient's age at hemorrhagic manifestation.

Aim. to develop a method for individual prediction of the cAVM risk rupture during the natural course of the disease.

Material and methods. A retrospective analysis of demographic characteristics, clinical manifestations, and instrumental research data was performed in 104 patients with cAVM who underwent treatment from 2011 to 2023.

Results. Hemorrhage occurred in 40 (38.5 %) of 104 patients, while in 35 (33.7 %) patients it was the first manifestation of cAVM. The median age of patients at time of cAVM rupture was 55 (95 % CI 49–61) years. A new method for predicting the risks of cAVM rupture was developed based on 4 factors that were identified as a result of regression analysis and rupture risk analysis (Cox and Weibull models), as well as clinical considerations. The developed DSSF scale takes into account the following parameters: deep outflow deficit ($p = 0.022$), maximal node size ($p = 0.012$), side of cAVM location ($p = 0.014$), absence of fistula ($p = 0.072$). Patients can be divided into 3 categories based on the sum of points obtained while assessing 4 characteristics of cAVM using the DSSF scale. The proposed cAVM assessment system was the following: +3 points – left side of the brain; – 1 point – maximum size of the cAVM node per each 1 cm; +4 points – deep outflow deficiency; +2 points – absence of fistula. The low-risk group (group A) included patients with the following set of parameters: – 2 points or less for cAVM; 43 % of the sample; median patients' age at the time of cAVM rupture – 64 [60, 72] years. The moderate risk group (B) included the following parameters: from –1 to +1 points for cAVM; 39.4 % of the sample; median patients' age at the time of cAVM rupture – 50 [44, 59] years. The high risk group (C) included the following parameters: +2 or more points for cAVM; 17.3 % of the sample; median patients' age at the time of cAVM rupture – 38 [30, 48] years. The risk of hemorrhage from cAVM for patients in group A was 0 at 20; 8 at 30; 12 at 40; 17 at 50; 17 % at 60 years old. In the same age categories, these data for group B were 0, 8, 19, 41 and 80 %, for group C – 11, 29, 60, 79 % and about 100 %.

Conclusion. The proposed method for assessing the hemorrhage risk for cAVM allows ranking patients into groups with low, moderate or high risk of intracranial bleeding, suggesting the patients' age at time of cAVM rupture and choosing the adequate treatment tactics in terms of surgical aggression and time to cAVM elimination.

Keywords: cerebral arteriovenous malformation (cAVM), intracranial hemorrhage, hemorrhage risk, hemorrhage predictor, cAVM rupture risk, deep cerebral vein drainage, fistula, optimized treatment strategy, size of cerebral AVM, patient's age

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BACKGROUND

Early publications (1988) indicate severe outcomes of hemorrhage from cerebral arteriovenous malformation (cAVM). The hemorrhage occurred in 18.5 % of 162 patients (mean follow-up duration 8.2 years), the mortality after rupture reached 29 %, the risk of significant disability among survivors was 23 % [1].

While analyzing the outcomes of hemorrhage from cAVM in modern conditions (2020), the risk of hemorrhage remains quite high. The mortality after cAVM rupture is 21 %, the moderate or severe neurological deficit is developed in 26 % of patients, while previously performed embolization or treatment with a gamma knife did not affect the clinical outcome [2]. Obviously, the outcomes after hemorrhage from cAVM remain unfavorable for more than 30 years, despite significant progress in their treatment. It should be noted that hemorrhage from cAVM during multi-stage multimodal treatment has the same structure of outcomes.

It is noteworthy that the first and repeated hemorrhages from cAVM have an equally unfavorable effect on the functional status. In those patients admitted with hemorrhage as the primary cAVM manifestation, the proportion of patients with mRs[1] 0–2 points decreased by the time of discharge from 100 to 67 %, i. e., the disabling neurological deficit developed in 33 % of patients. After the second hemorrhage, the proportion of patients with mRs 0–2 points at discharge decreased from 97 to 66 %, i. e., the disabling neurological deficit developed in 31 %.

In the group of patients with nonhemorrhagic cAVM manifestation who subsequently suffered from intracranial hemorrhage, the proportion of patients with mRs 0–2 points decreased from 100 % during admission to hospital to 56 % at discharge, i. e. the disabling neurological deficit developed in 44 % of patients [3]. The absence of an effect of previously hemorrhage from cAVM on the clinical outcome of the subsequent hemorrhages is also confirmed by other authors [2].

Thus, the hemorrhage from cAVM is an event that has a catastrophic effect on the functional status of the patient, regardless of the type of cAVM manifestation and the fact of previous hemorrhages.

It is worth noting the one of the findings (and its influence) of the final analysis of the multicenter randomized ARUBA trial published in 2020. The conservative treatment of patients with unruptured cAVMs showed its advantage over any type of intervention in terms of death or symptomatic stroke [4]. Although the results of this study have been repeatedly questioned in subsequent years, this publication probably had negative consequences. The publication of ARUBA trial results led to an increase in the proportion of patients admitted to hospitals already with cAVM hemorrhage (apparently against the decreasing of surgical activity in patients with unruptured cAVM) [5–7].

Obviously, the progress in surgical treatment of cAVM and achievements in anesthesiology as well as in intensive-care medicine make it possible to eliminate cAVM with an acceptable risk before intracranial hemorrhage. This should be considered as another argument for choosing an active treatment strategy in patients with cAVM. However, given the uncertainty of the prognosis of the cAVM course in a particular patient, the choice of the optimal combination of treatment methods is currently based more on the morphological characteristics and clinical manifestations of cAVM than on individual prediction of the hemorrhage risk.

This state of affairs and the need to select the most effective and rapid method of treatment (or a sequential combination of methods, hybrid intervention) in patients, who obviously have a high risk of intracranial hemorrhage, make us think about a prompt and clear assessment of the patient's condition and the risk of cAVM rupture. This individual assessment of the hemorrhage risk from the cAVM will allow us to select the most adequate treatment tactics taking into account the expected risk of cAVM rupture and patients' age at time of hemorrhagic manifestation of the disease.

The aim of the conducted study was to develop a method for individual prediction of the rupture risk of cAVM during the natural course of the disease.

MATERIAL AND METHODS

The retrospective analysis of demographic characteristics, clinical manifestations, and instrumental examination data was performed in 104 patients diagnosed with "cerebral arteriovenous malformation" in the period from 2011 to 2023. The natural history period was defined as the time interval from birth to any intervention (microsurgical, endovascular, or radiosurgical) on cAVM. Depending on the presence of an established fact of intracranial hemorrhage from cAVM, patients were divided into two groups – those who had hemorrhage during the natural course of the disease (H+) and those who did not (H–).

The demographic, clinical, anatomical and hemodynamic characteristics of 104 patients (30 women and 74 men) were collected and analyzed. The mean patients' age at the time of cAVM diagnosis (manifestation or detection in asymptomatic course) was 36.2 ± 13.9 years old.

The detailed data of the patients included in the study (in the fact of previous hemorrhage) and the cAVM characteristics are presented in Table 1 and analyzed below.

There is a higher frequency (65 %) of cAVM in the left cerebral hemisphere in the group of patients having a hemorrhage (H+) as can be seen in Table 1. Among patients with the hemorrhagic type of cAVM, the disease was diagnosed later than in the group without hemorrhagic manifestations (40.1 *vs* 33.7 years); at the time of the initial examination at the hospital, the functional state of patients who had a hemorrhage from cAVM (H+) was significantly worse (mRS 1.3 *vs* 0.9 points).

In cases without hemorrhagic manifestations, patients with a torpid type of course dominated (93.8 %), among the first clinical manifestations were a seizure (48.4 %) and headache (34.4 %). It is noteworthy that before the development of hemorrhage, cAVM manifested (and was diagnosed) with a seizure in 7.5 % of cases as well as with headache – in 5 % of patients. Therefore, theoretically it was possible to prevent hemorrhage in cases of cAVM detection, as well as to eliminate malformations in the prehemorrhagic period.

The localization of cAVM in both groups did not differ significantly, in 50 % of cases they were located outside the functionally significant areas. While localizing in the

[1]mRS (modified Rankin Scale) – the modified Rankin Scale that evaluates (in points) the degree of disability and dependence in the daily activities of the patients, rehabilitation outcomes.

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Table 1. Clinical and demographic characteristics of patients with cerebral arteriovenous malformation

Characteristic	Value*	H– (*n* = 64)	H+ (*n* = 40)	Total	*p*
Gender	F	20 (31.2)	10 (25.0)	30 (28.8)	0.644
	M	44 (68.8)	30 (75.0)	74 (71.2)	
Localization of cAVM (cerebral hemisphere)	Left	26 (40.6)	26 (65.0)	52 (50.0)	0.027
	Right	38 (59.4)	14 (35.0)	52 (50.0)	
Dominant cerebral hemisphere	Left-handed	2 (3.2)	–	2 (2.0)	0.242
	Right-handed	60 (96.8)	39 (97.5)	99 (97.1)	
	Ambidexter	–	1 (2.5)	1 (1.0)	
Patients' age at the time of cAVM manifestation or detection, years old	Mean (SD)	33.7 (12.9)	40.1 (14.8)	36.2 (13.9)	0.022
mRs at the time of initial examination	Mean (SD)	0.9 (0.5)	1.3 (0.8)	1.0 (0.7)	0.001
Type of disease course	Asymptomatic	4 (6.2)	–	4 (3.8)	<0.001
	Torpid	60 (93.8)	–	60 (57.7)	
	Hemorrhagic	–	40 (100.0)	40 (38.5)	
Initial manifestation	Asymptomatic	4 (6.2)	–	4 (3.8)	<0.001
	Headache	22 (34.4)	2 (5.0)	24 (23.1)	
	Focal neurological deficit	7 (10.9)	–	7 (6.7)	
	Seizure disorders	31 (48.4)	3 (7.5)	34 (32.7)	
	Hemorrhage	–	35 (87.5)	35 (33.7)	
Localization of cAVM in functionally significant area	cAVM is out of functionally significant area	32 (50.0)	20 (50.0)	52 (50.0)	0.624
	Motor or sensor cortex	18 (28.1)	8 (20.0)	26 (25.0)	
	Visual cortex	11 (17.2)	9 (22.5)	20 (19.2)	
	Cortical speech areas	2 (3.1)	3 (7.5)	5 (4.8)	
Seizure disorders	Presence	34 (53.1)	7 (17.5)	41 (39.4)	0.001
Headache	Presence	26 (40.6)	1 (2.5)	27 (26.0)	<0.001
Focal neurological deficit	Presence	8 (12.5)	1 (2.5)	9 (8.7)	0.160

Note. *The groups of patients in the natural course of the disease: (H –) – without hemorrhage, (H+) – with hemorrhage. mRS – assessment of disability, independence, and rehabilitation outcomes according to the modified Rankin scale; p – criteria: Chi-square – for categorical variables, Fisher – for continuous variables. cAVM – cerebral arteriovenous malformation; (–) – absence of patients with such a characteristic in the group.*
**The values of characteristics: continuous numerical – mean (and standard) deviation Mean (SD); qualitative characteristics – absolute and relative number of patients in the group n (%).*

functionally significant area, cAVM was found somewhat more often in the motor or sensory cortex in patients without hemorrhage (H–), but in the visual and speech cortex in patients with hemorrhage (H+) without statistically significant differences ($p = 0.624$). The seizure disorders and headache (53.1 and 40.6 %, respectively) were significantly more often observed in patients without cAVM rupture.

Statistical data processing. It was performed by means of the R language (version 4.4.3) in the RStudio environment (version 2023.06.0+421 (2022) by Posit Software, PBC) using descriptive statistics methods, Chi-square and Fisher criteria, survival analysis using a semiparametric proportional hazards model (Cox regression) and a parametric model (Weibull).

RESULTS

The analysis of the qualitative and quantitative characteristics of cAVM was performed to identify the significant factors influencing the risk of hemorrhage. The results of univariate and multivariate regressions with the inclusion of the most significant factors (cAVM

pathophysiology and statistical analysis) are presented in Table 2.

The univariate regression analysis of cAVM characteristics revealed the most significant features influencing the risk of hemorrhage from cAVM (see Table 2):

- maximal size and volume of cAVM;
- side of the lesion;
- type of structure (presence of a fistula in the structure of cAVM);
- number of feeding branches (afferents);
- number of outgoing veins (efferents).

Taking into account the statistical significance and clinical considerations, only 4 characteristics were included in the final version of the proposed DSSF model:

1) deep outflow **d**eficit;
2) maximal **s**ize of cAVM;
3) **s**ide of the lesion;
4) absence/presence of **f**istula.

The model is applicable for describing the risk of hemorrhagic manifestations of cAVM throughout the entire observation period ($p = 0.82$). The exclusion of such parameters from the model as the number of branches entering the cAVM and the number of outgoing veins did not affect its accuracy (ANOVA $p = 0.63$), while it is necessary to note the presence of a statistically significant complex interaction of the two specified factors within the full model ($p = 0.041$), which may in the future become the subject of a separate study.

1. Deep outflow deficit. The absence of deep outflow deficit reduced the risk of hemorrhagic manifestation of cAVM (Cox proportional hazards model HR = 0.25, $p = 0.022$). The effect of the factor was uniform over time ($p = 0.73$). The absence of deep outflow deficit in cAVM increased the time to rupture by 36.2 % (95 % CI 3.9–78.6 %), the risk of rupture was lower by 71.1 % (95 % CI 11.7–90.6 %) with correction for the side of the lesion, maximum size and the presence of a fistula.

2. Maximal size. The increase in the cAVM size led to the decrease in the risk of hemorrhagic manifestations (Cox proportional hazards model HR = 0.67, $p = 0.012$). The effect of this factor was uniform over time ($p = 0.40$). The increase per each 1 cm in the maximal cAVM size increased the time to rupture by 7.1 % (95 % CI 0.4–15.2 %), the risk of rupture was lower by 24.2 % (95 % CI 0–43.2 %) with adjustment for the side of the lesion, the presence of deep outflow deficiency and fistula.

3. Side of the lesion. In our model, the location of cAVM in the right cerebral hemisphere decreased the risk of hemorrhagic manifestation (Cox proportional hazards model HR = 0.41, $p = 0.014$). The effect of this factor was uniform over time ($p = 0.34$). The location of cAVM in the right cerebral hemisphere increased the time to rupture by 22.1 % (95 % CI 2.7–45.2 %), the risk of rupture was lower by 55.2 % (95 % CI 11.1–77.4 %) with adjustment for maximal size, presence of deep outflow deficit and fistula.

4. Absence/presence of fistula. The presence of fistula reduced the risk of hemorrhagic manifestation of cAVM (Cox proportional hazards model HR = 0.52, $p = 0.072$). The effect of this factor was uniform over time ($p = 0.79$). The presence of fistula in the cAVM structure increased the time to rupture by 18.8 % (95 % CI 0.0–41.2 %), the risk of rupture was lower by 50.0 % (95 % CI 11.7–89.9 %) with correction for the side of the lesion, maximal size and the presence of deep outflow deficit.

Based on the data obtained from the regression analysis and rupture risk analysis (Cox and Weibull models), we developed a scale for assessing the risk of a hemorrhagic event in patients with cerebral cAVM (Table 3). The DSSF scale takes into account:

1) deep outflow deficit ($p = 0.022$);
2) maximal node size ($p = 0.012$);
3) side of cAVM location ($p = 0.014$);
4) absence of fistula ($p = 0.072$).

Based on the sum of the scores obtained while assessing these four characteristics of cAVM, as well as taking into account the sample (%) and patients' age at the time of cAVM rupture, patients can be divided into 3 groups: A – with a low risk of cAVM rupture; B – with a moderate risk; C – with a high risk (Table 4).

In the total sample, the median patients' age at the time of cAVM rupture was 55 (95 % CI 49–61) years old. As can be seen from Table 4, the largest group in our sample consists of patients with low-risk cerebral cAVMs – group A (43.3 %). The median patients' age at the time of cAVM rupture in this group was 64 years, and the interquartile range (60–72 years) is within the elderly age range (60–74 years, according to WHO recommendations).

The second largest group (with a moderate risk of cAVM rupture) is group B (39.4 %). The median patients' age at the time of cAVM rupture in this group was 50 years old, the interquartile range (44–59 years) is within the average age (45–59 years, according to WHO recommendations). The risk of cAVM rupture for group B statistically significantly exceeds this value for group A (by 3.21 times).

The high risk of cAVM rupture, according to the developed scale, was present in 17.3 % of patients in group C. The median patients' age at the time of cAVM rupture in this group was 38 years old, the interquartile range (30–48 years) refers mainly to the second half of young age (18–44 years, according to WHO recommendations). The risk of cAVM rupture for group C statistically significantly exceeds this value for group A (by 10.4 times).

The data of the cumulative incidence of hemorrhages from cAVM of different grades and the patients' age of hemorrhage occurrence are shown in Fig. 1. Thus, the cumulative incidence and risk of hemorrhage from cAVM significantly differed between the groups. For example, before reaching the age of 40 years old in patients of group A, cAVM will prognostically rupture in an average of 12 % of patients (95 % CI 4–26 %), in group B – in 19 % (95 %

Table 2. The influence of cerebral arteriovenous malformation characteristics on the risk of its rupture

Characteristic	Value*	Risk ratio (Cox proportional hazards model HR)	
		univariate model	incomplete multivariate model (DSSF)
Volume, cm^3	17.7 (20.8)	0.97 (0.94–0.99, $p = 0.013$)	–
Maximal size, cm	3.5 (1.4)	0.63 (0.47–0.84, $p = 0.002$)	0.67 (0.48–0.91, $p = 0.012$)
Side: left right	 52 (50.0) 52 (50.0)	 Reference value** 0.51 (0.26–0.98, $p = 0.045$)	 – 0.41 (0.20–0.83, $p = 0.014$)
Type of cAVM: racemose mixed fistulous	 32 (30.8) 57 (54.8) 15 (14.4)	 Reference value** 0.39 (0.19–0.79, $p = 0.009$) 0.50 (0.19–1.30, $p = 0.154$)	 – – –
Fistula	72 (69.2)	0.41 (0.21–0.80, $p = 0.009$)	0.52 (0.25–1.06, $p = 0.072$)
Type of cAVM node***: diffuse compact	 20 (19.2) 84 (80.8)	 Reference value** 1.19 (0.52–2.74, $p = 0.675$)	 – –
Intranidal aneurysm(s)	14 (13.6)	1.32 (0.57–3.04, $p = 0.512$)	–
Non-flow-related aneurysm(s)	8 (7.8)	0.64 (0.24–1.69, $p = 0.369$)	–
Flow-related aneurysm(s)****: proximal distal	10 (9.6) 4 (3.8) 6 (5.8)	1.12 (0.40–3.19, $p = 0.825$) 0.81 (0.11–6.02, $p = 0.840$) 1.29 (0.39–4.25, $p = 0.678$)	– – –
Component of cAVM: sulcal gyral subcortical paraventricular	 7 (6.7) 97 (93.3) 44 (42.3) 12 (11.5)	 0.65 (0.16–2.73, $p = 0.561$) 0.70 (0.25–1.98, $p = 0.499$) 0.80 (0.41–1.55, $p = 0.502$) 0.75 (0.26–2.13, $p = 0.584$)	 – – – –
Number of vessels: feeding arteries afferents – superficial – deep	 2.1 (0.9) 3.6 (1.9) 1.8 (0.9) 0.2 (0.5)	 0.80 (0.53–1.23, $p = 0.315$) 0.75 (0.58–0.96, $p = 0.025$) 0.79 (0.53–1.17, $p = 0.236$) 1.25 (0.57–2.75, $p = 0.583$)	 – – – –
Type of cAVM venous drainage: deep deep + superficial superficial	 4 (3.8) 23 (22.1) 77 (74.0)	 Reference value** 0.34 (0.04–2.99, $p = 0.328$) 0.57 (0.07–4.30, $p = 0.582$)	 – – –
Number of veins from cAVM	1.7 (0.7)	0.66 (0.42–1.03, $p = 0.069$)	–
Venous ectasia	0.3 (0.6)	0.78 (0.45–1.37, $p = 0.389$)	–
Drainage veins, reaching the sinus (large vein)	1.7 (0.7)	0.71 (0.46–1.11, $p = 0.138$)	–
Without deep outflow deficit	93 (89.4)	0.51 (0.18–1.49, $p = 0.220$)	0.25 (0.08–0.81, $p = 0.020$)

Note. *DSSF is the name of the scale (acronym) that takes into account the following four factors: deep outflow **d**eficit, maximal node **s**ize, **s**ide of cAVM location, absence/presence of **f**istula (the name of the model in the Russian language was also chosen due to the coincidence with the name "dimethyl sulfoxide" – a solvent used in embolizates for the treatment of AVM); cAVM – cerebral arteriovenous malformation; (–) not calculated, since the proposed DSSF model takes into account only 4 characteristics.*

**The values of characteristics: continuous numerical – mean (and standard) deviation Mean (SD); qualitative characteristics – absolute and relative number of patients in the group n (%).*

***The reference value was taken as the value relative to which the risk ratio in other groups was calculated.*

****Compact cAVMs do not contain brain matter between the vessels of the malformation node, while in diffuse cAVMs the malformation node contains brain matter.*

*****The proximal cAVMs are located on the main vessels before the level of their bifurcation, the distal ones are located on the distal segments of the afferent vessels.*

Table 3. DSSF scoring system for risk assessment of cerebral arteriovenous malformation rupture

Factors of DSSF scale	Characteristic	Contribution into the assessment of cAVM risk rupture, points
Deep outflow **d**eficit	Presence of deep afferent and absence of deep drainage vein	+4
Maximal **s**ize of cAVM node, cm	1 point for each 1 cm	–1
Side of cAVM location	Left cerebral hemisphere	+3
Absence of **f**istula	Racemose type of cAVM, absence of a direct fistula	+2

Note. *See note to Table 2.*

Table 4. Characteristics of the risk of cerebral arteriovenous malformation rupture (DSSF scale grades)

Category (group)	Total score	Number of patients, *n* (%)	HR	95 % CI	*P*-value	Patients' age at the time of cAVM rupture		Rupture risk of cAVM
						In cohort, Me [Q1, Q3] (years old)	Expected (according to DSSF scale)	
A	–2 and less	45 (43,3 %)	Reference value*	Reference value*	Reference value*	64 [60, 72]	Elderly	Low
B	from –1 to +1	41 (39,4 %)	3.21	1.35, 7.64	0.008	50 [44, 59]	Average	Moderate
C	More than +1	18 (17,3 %)	10.4	3.98, 27.2	<0.001	38 [30, 48]	Young	High

Note. *HR is an estimation from the proportional hazards model (Cox regression). See note to Table 2.*
**The risk ratios for group A were taken as reference, and the values in groups B and C were calculated relative to those for group A.*

CI 7–35 %), and in group C – in 60 % (95 % CI 31–80 %). These findings we consider as the indication for active surgical treatment tactics for patients in group C as well as for the selection of methods (or a combination of methods) which will lead to the rapid and complete elimination of cAVM before its rupture.

DISCUSSION

The information about the type of clinical manifestation of cAVM from the literature and from our observation series is presented in Table 5. As it can be seen from these data, the first manifestation of 1/3 to 1/2 of all cAVMs is the intracranial hemorrhage, and the average patients' age at the time of cAVM manifestation (for all types of clinical course) is within 34–38 years old.

It should be noted that in our series of observations (see Table 5), the proportion of patients with hemorrhagic manifestation of cAVM was slightly lower (33.7 %), and with a seizure and headache was higher (32.7 and 23.1 %, respectively) compared with similar series of 2004–2006 [3, 8]. These differences are probably due to the higher availability of diagnostic methods (firstly MRI of the brain) in our series of observations (2024), which led to the diagnosis of cAVM in the pre-hemorrhagic period during an examination prescribed for minimal indications (for example, due to complaints of headache) or for another reason.

According to the results of the data analysis in 790 patients (Kaiser Permanente Northern California Health Maintenance Organization), the only statistically significant predictor of hemorrhage from cAVM was a previous hemorrhage, with the risk of recurrent hemorrhage reaching 7 % in the first year and decreasing to 3 % per year thereafter [3]. The increase of the hemorrhage risk with increasing the patients' age was also noted, although the influence of this factor was at the border of statistical significance [3].

Although the proportion of patients with cAVM hemorrhage was higher in the colored (non-white) group (38 *vs* 25 %), the subsequent stratified analysis revealed no differences in the risk of hemorrhage between ethnic groups [3].

In the series of observations from the prospective Columbia AVM database [8], the attention was drawn to particularly unfavorable combinations of factors for hemorrhage from cAVM. For example, in a group of patients with deep localization of cAVM and exclusively deep venous outflow with hemorrhagic manifestation, the annual risk of recurrent hemorrhage was 34.3 %, and in the absence of all three of these signs – only 0.9 % per year [8]. The feature of the Columbia AVM database is a fairly large number of deep and infratentorial cAVMs – 9 and 12 %, respectively. In our study, cAVMs of similar characteristics were found in a different ratio – 11.5 and 1.9 %.

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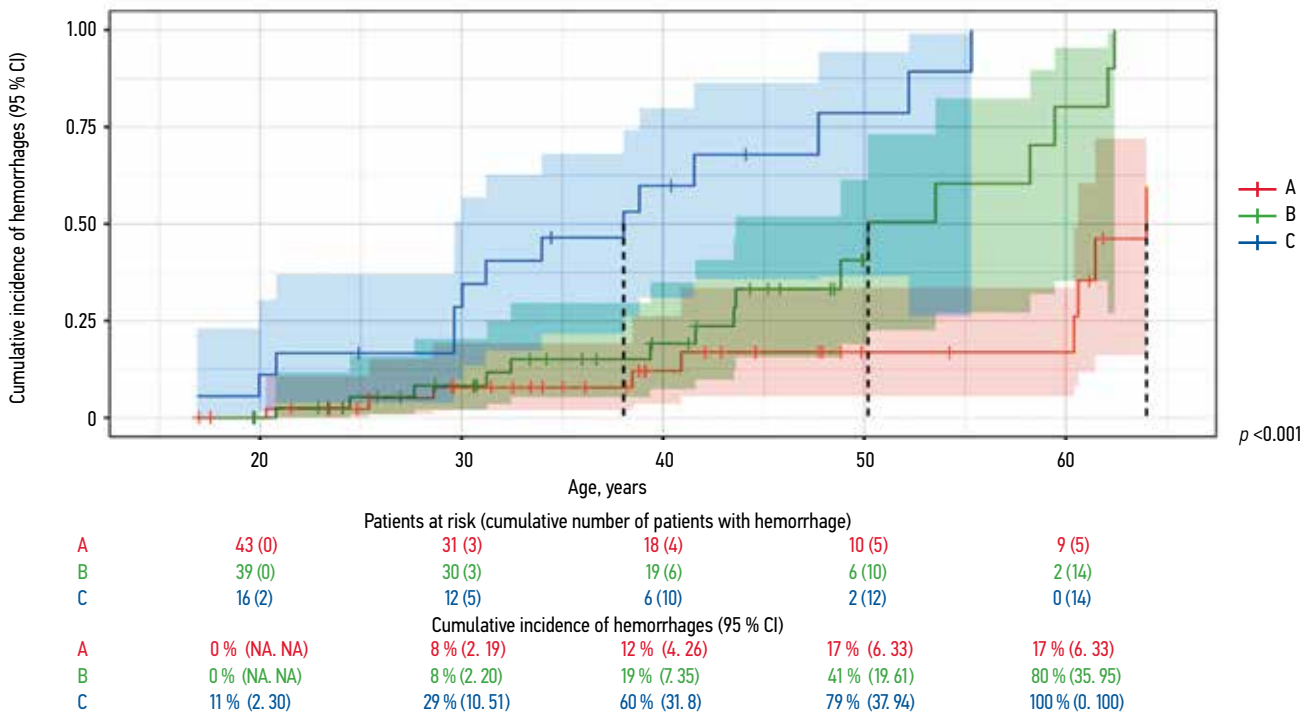

Fig. 1. *The prediction of the cumulative risk of cerebral arteriovenous malformation rupture for different categories of patients: A – with low risk; B – with moderate risk; C – with high risk. Data of 104 patients during the period 2011–2023 were assessed using the developed DSSF scale (see note to Table 2). The graphical interface of the RStudio environment (version 2023.06.0+421 (2022), Posit Software, PBC) reflects the results of data analysis, version 4.4.3, tidycmprsk package 1.1.0). NA (not available) – the indicator cannot be calculated*

Table 5. Clinical manifestation of cerebral arteriovenous malformation

Clinical manifestation of cAVM	Source data			
	Kaiser Permanente Northern California Health Maintenance Organization (*n* = 790) [3], 2004	Columbia AVM database (*n* = 662) [8], 2006	Meta-analysis (*n* = 3923) [8], 2012	Our observation series (*n* = 104), 2024
Patients' age at the time of cAVM manifestation (mean, years old)	38 (95% CI 33.7–39.3)	34 (95% CI 32.9–35.2)	33,7 (95% CI 31.1–36.2)	36,2 (95% CI 33.5–38.9)
Hemorrhage, %	47	45	52	33.7
Seizure disorders, %	24	29	27	32.7
Headache, %	14	13	–	23.1
Focal neurological deficit, %	–	7	–	6.7
Others, %	15	6	–	–
Asymptomatic disease course, %	–		–	3.8

Note. *(–) there are no available data. See note to Table 2.*

The average patients' age at the time of cAVM manifestation, according to a large meta-analysis, was 33.7 years old, and risk-increasing factors included previous hemorrhage, deep localization, exceptionally deep venous outflow, and associated aneurysms [9]. Among patients with nonhemorrhagic manifestation of cAVM, the hemorrhage developed later in 8 % of cases (in our series, in 12.5 % of cases) as well as the median to rupture was 3.7 years [3].

The risk factors for hemorrhagic manifestation of cAVM according to literature data and in our series are presented in Table 6, a number of classifications for formalized individual assessment of the risk of hemorrhage from cAVM are presented in Table 7.

The calculation method of D. Kondziolka et al. [10], based on the annual risk of hemorrhage from cAVM, does not take into account the heterogeneity of this pathology

and excludes an individualized prognosis, answering only the question about the proportion of patients with hemorrhagic manifestation of cAVM in the total sample of patients over time.

The method of U. Mansmann et al. [11] for individual assessment of the risk of hemorrhagic manifestation of cAVM is based on taking into account 10 different factors and their mutual influence, but the calculation process is quite labor-intensive.

The method of F. Nataf et al. [12] for assessing the risk of hemorrhage from cAVM is based primarily on the assessment of venous outflow characteristics and scoring with the allocation of a very high-risk group (>1 point). However, in the remaining group (from –1 to +1 point), a large error in assessing the risk of hemorrhage was observed, i. e. this technique did not allow assessing the real risk of hemorrhage from cAVM. In our opinion, the method proposed by F. Nataf et al. has low practical value, since patients who are not classified as very high risk according to this scale may still have a real (and even high) risk of hemorrhage, and such underestimation is dangerous.

Table 6. The risk factors for cerebral arteriovenous malformation hemorrhage

Study	Factors		
	Increasing the risk rupture	**Decreasing the risk rupture**	**Indifferent**
1997 F. Nataf et al. (*n* =160)*	Only deep venous drainage; venous stenosis; venous reflux into sinus or into deep vein; involvement of nontypical venous drainage routes	–	–
2004 A.X. Halim et al. (*n* = 176)*	Hemorrhagic manifestation	–	Gender; ethnic affiliation; size of cavm; only deep venous drainage
2006 C. Stapf et al. (*n* = 622)*	Age; previous hemorrhage; deep localization; only deep venous drainage	–	Gender; size of cavm; intranidal aneurysm or aneurysm on feeding artery
2012 B.A. Gross et al. (*n* = 3923)**	Previous hemorrhage; deep localization; only deep venous drainage; flow-related aneurysms	–	Gender; Size of cAVM <3 cm; elder age
2017 F. Padilla-Vazquez et al. (*n* = 639)*	Average flow velocity in the main afferent; type of venous drainage; size of cAVM <3 cm	–	–
2000 U. Mansman*n* et al. (*n* = 662)*	Deep venous drainage; deep localization; corticocallosal localization; posterior cranial fossa localization	Arterial stenosis; venous ectasia; arteriovenous fistula; proximal aneurysm	–
2024 B. G. de Liyis at al. (*n* = 4240)**, repeated hemorrhages	Previous hemorrhage; deep venous drainage; flow-related aneurysms	Volume of cAVM: the more the volume – the less the rupture risk; The higher score according to Spetzler – Martin – the less the rupture risk	–
2024 (*n* = 104), our observatio*n* series*	Left cerebral hemisphere; deep outflow deficit	Maximal size and volume of cAVM: decreasing the rupture risk while these parameters are increasing; Presence of fistula. The more the number of afferents – the lower the risk of hemorrhage. The more the number of drainage veins – the less the rupture risk	Gender; Localization in relation to cortex/white matter/ventricles; Intranidal aneurysms; non-flow-related aneurysms; flow-related aneurysms; Venous ectasia

Note. *(–) not found. See note to Table 5.*
**Multivariate regression analysis.*
***Meta-analysis of non-randomized studies.*

The interesting feature of the method is the use of a calculation parameter that is expressed as the ratio of the number of arteries feeding the cAVM to the number of drainage veins [12]. While analyzing our own data, we also found an effect of the number of afferents and efferents on the risk of hemorrhage from cAVM, but excluding these parameters did not affect the accuracy of our model. Moreover, we found an interaction between these two characteristics of cAVM, which could potentially form the basis of a method for determining the risk of hemorrhage, but in this article, we will refrain from a more in-depth analysis, leaving it for subsequent publications.

The classification by F. Padilla-Vazquez et al. [13] is based on the comprehensive approach taking into account Doppler ultrasound data (average flow velocity in the main afferent, threshold value is 90 cm/s), as well as the size of the cAVM (threshold value is 3 cm) and the type of venous outflow. The original classification is proposed 3 types of outflow with subtypes which depends on the direction of outflow and the involvement of superficial and deep veins. The authors identified 4 gradations of cAVM, differing in the risk and patients' age at the time of cAVM rupture. It is interesting that the Spetzler – Martin gradation of cAVM does not affect the risk of hemorrhage, according to the authors [13].

The R_2eD AVM Score (prediction of risks of cAVM rupture) method [14] is based on the analysis of 5 factors such as the race (white/color (non-white)), deep localization of cAVM, size of cAVM, exceptionally deep venous outflow, and mono-afferent type. This method is based on logistic regression, which considers two potential outcomes – the presence and absence of hemorrhage, and does not allow, unlike our method, to estimate the patients' age at the time of hemorrhagic manifestation of cAVM. In addition, such features as "deep localization" and "exceptionally deep venous outflow" in the R2eD AVM Score, in our opinion, partially duplicate each other.

The VALE scale (determination of the risk of hemorrhage from unruptured cAVMs) [15] evaluates 4 features such as the involvement of the ventricular system, presence of venous ectasia, deep localization and exceptionally deep venous outflow. As a result of the calculation, all patients, according to the VALE classification, can be divided into 3 risk groups – low, medium and high, with an average probability of a 10-year hemorrhage-free period of 95.5, 92.8 and 75.8 %, respectively [15].

The DSSF scale proposed by us (the assessment of the risk of hemorrhage from cAVM) is based on the factors that have a number of features.

Deficient of deep outflow from cAVM, by which we mean the presence of a "deep" afferent in the absence of deep venous outflow, served as a factor that reliably increased the risk of hemorrhagic manifestation of cAVM

Table 7. The methods for assessing and predicting the risk of hemorrhage in cerebral arteriovenous malformation

Authors, year	Factors	Gradation number	Validation	Name of method
F. Nataf et al., 1997	Only deep venous drainage; Venous stenosis; Venous reflux into sinus or into deep vein; Involvement of nontypical venous drainage routes Afferents/efferents ratio	3	No	–
U. Mansmann et al., 2000	Size of cAVM; Deep venous drainage; Cortical localization; Corticoventricular localization; Arterial stenosis; Dural venous stenosis; Arterial ectasia; Arteriovenous fistula; Intensity of angiogenesis	12	No	–
F. Padilla-Vazquez et al., 2017	Average flow velocity in the main afferent, type of venous drainage, size	4	No	Padilla
J. Feghali et al., 2019	Race (white/color (non-white), deep localization, size, only deep venous drainage, mono-afferent type of blood supply	5	Yes	R_2eD
Y. Chen et al., 2023	Involvement of ventricles, venous aneurysm, deep localizationa and only deep venous drainage	3	Yes	VALE
A.V. Savello et al., 2024	deep outflow **d**eficit; maximal **s**ize of cAVM; **s**ide of the lesion; absence/presence of **f**istula	3	No	DSSF

Note. *See note to Table 3.*

in our observational series. It should be noted that all cAVMs that had a deficit of deep outflow had a deeply located compartment.

The size of the cAVM node (and its volume) have previously been identified in a number of studies as characteristics influencing the risk of hemorrhage [13, 16], however, in other large series, the effect of size on the risk of hemorrhage was not established [3, 8, 9]. In our study, the size of the cAVM and the risk of hemorrhage had an inverse relationship – the smaller malformations had a higher risk of hemorrhagic manifestation.

Thus, the side of the cAVM location in our observation series unexpectedly turned out to be a significant predictor of the rupture risk. It should be noted that in the studied literature this sign was not included in the list of analyzed characteristics at all [11, 12, 14, 15] and therefore its influence was not assessed. It cannot be ruled out that the higher risk of cAVM rupture in the left cerebral hemisphere observed in our series is due to a higher probability of clinically manifest hemorrhage in the dominant hemisphere, which leads to timely examination of the patient and detection of cAVM and hemorrhage in CT or MRI.

The presence of a fistula in the cAVM structure has previously been identified as a factor influencing the risk of hemorrhagic manifestation [11]. In our series, cAVMs with a fistula had a lower risk of rupture, probably due to a decrease in the static pressure of the flowing blood in the malformation node.

It should be noted that long-term observation of patients with cAVM to study changes in its morphology and hemodynamics during life seems unethical to us. It is necessary to take into account the high risks of cAVM rupture and the adverse consequences of this event [2], as well as the patient's wishes for active treatment tactics.

The stability of the characteristics. How stable are the characteristics underlying the proposed DSSF classification? Can the risk of hemorrhage from cAVM change after examination? The side of cAVM location obviously cannot change during the course of the disease. The such characteristics as maximal size and presence of fistula can theoretically change depending on the severity of neoangiogenesis and increase in the intensity of arteriovenous shunting, however, the stability of these characteristics, molecular genetic mechanisms of progression, the role of hypoxia, and even the congenital nature of cAVM itself are highly discussable. In the literature, an increase in the size of a cAVM is considered as a rare event that can occur before the age of 30 years old with an unknown frequency, and the most of the described cases of the "appearing" of new cAVMs (or a significant increase in the size and nature of drainage) relate to adolescence [17, 18]. The occurrence of a deep outflow deficit is possible with thrombosis of a deep draining vein against the background of its damage by the blood flow, which in itself can manifest as a hemorrhage.

Thus, 3 of the 4 characteristics of cAVM, which form the basis of the proposed DSSF classification, are stable in adult patients, for whom the risk assessment scale for hemorrhagic manifestation of cAVM was developed. An objective assessment of cAVM by the three proposed characteristics (side, size, presence of deep outflow deficiency) does not cause difficulties. The detection of the fistula component of cAVM is subjective, but it is widely used both in our observation series and in the studies of other authors. We will only note that the detection of a fistula in the cAVM structure is reliably possible only according to the data of digital subtraction cerebral angiography.

Assumptions and limitations of the study

1. It was assumed in our study, that cerebral AVM is a congenital pathology, although there are individual clinical observations and series indicating the possibility of the appearance of cAVM *de novo* [17, 18].
2. The second important assumption is the constancy of the properties of the cAVM included in the model throughout adult life.
3. This model is not intended to assess the risks of hemorrhage from cAVM in children. Taking into account the age of patients treated at the Medical Military Academy and the Almazov National Medical Research Center (Saint Petersburg, Russia), the model we developed for predicting hemorrhage from cerebral AVM can be used within the age of disease detection, i. e., 15–65 years.
4. The results of the study are limited to a group of patients who sought treatment at a specialized hospital. It is possible that the characteristics of patients admitted to neurosurgical departments of our country for emergency indications differ from those obtained by us, and the model we proposed requires verification on a wider group of patients. For the same reason, the patients with unoperable widespread cAVMs, in particular with malformations of the basal ganglia and brainstem localization, were not included in the analysis.
5. The list of characteristics available for assessment in clinical practice is limited, so we relied only on these properties of cAVM, taking into account the recommendations for their description [19]. It is possible that some genetic, biochemical, hemodynamic and other characteristics that are currently unavailable for registration in routine clinical practice are also important for assessing the risk of hemorrhage from cAVM.

CONCLUSION

The proposed method for assessing the risk of hemorrhage from cAVM allows us to classify a patient into one of three groups: low (A), moderate (B), and high (C) risk. The method allows us not only to assess the risk of rupture, but also to assume the most probable patients'

age at which cAVM is most likely to lead to intracranial hemorrhage with potentially disabling and life-threatening consequences.

In patients with a high risk of cAVM rupture, it is obviously advisable to adhere to an active treatment strategy aimed to the rapid elimination of cAVM at a young patient's age. The multistage and/or combined treatment, spread over months and years, is acceptable for patients with a moderate or low risk of rupture (taking into account the patient's age). At the same time, it is necessary to consider the risks of cAVM modification during multistage treatment, which contribute to an increased risk of hemorrhage. Perhaps, in patients with a low risk of rupture, observation is also acceptable, since, according to our data, even by the age of 60, the proportion of patients with ruptured cAVMs in group A was about 17 %.

Using our method of assessing the risk of natural course, the tactics of cAVM elimination can also be selected from aggressive rapid at a young age to multi-stage long-term (potentially moving to observation while increasing patient's age). At the same time, generally accepted characteristics of cAVM, such as size, localization, nature of arterial inflow and venous outflow, etc., certainly remain important for choosing the optimal volume and sequence of therapeutic interventions (microsurgical, radiosurgical and endovascular).

The proposed method of individual assessment of the hemorrhage risk from cAVM allows us to classify a patient into a group with a low, moderate or high risk of intracranial hemorrhage, to assume the patient's age at the time of possible cAVM rupture and to choose a treatment tactic that is adequate in aggression and time until the elimination of cAVM.

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