Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

Nicollas Nunes Rabelo, Leonardo Zumerkorn Pipek, Rafaela Farias Vidigal Nascimento, João Paulo Mota Telles, Natalia Camargo Barbato, Antônio Carlos Samaia da Silva Coelho, Guilherme Bitencourt Barbosa, Marcia Harumy Yoshikawa, Manoel Jacobsen Teixeira, Eberval Gadelha Figueiredo

1. PhD. Universidade de São Paulo – Department of Neurosurgery – São Paulo (SP), Brazil.
2. Graduate student. Universidade de São Paulo – Faculdade de Medicina – São Paulo (SP), Brazil.
3. Graduate student. Faculdade de Medicina do ABC – Centro Universitário Saúde ABC – Santo André (SP), Brazil.

ABSTRACT

Purpose: To analyze the role of serum creatinine levels as a biomarker of intracranial aneurysm outcomes. Methods: This is a prospective analysis of outcomes of patients with intracranial aneurysm. One hundred forty-seven patients with serum creatinine at admission and 6 months follow up were included. Linear and logistic regressions were used to analyze the data. Modified Rankin scale (mRS) was used to assess outcome. Results: Creatinine level was not directly related to aneurysm outcome nor aneurysm rupture (p > 0.05). However, patients with a glomerular filtration rate (GFR) lower than 72.50 mL·min⁻¹ had an odds ratio (OR) of 3.049 (p = 0.006) for worse outcome. Similarly, aneurysm rupture had an OR of 2.957 (p = 0.014) for worse outcomes. Stepwise selection model selected 4 variables for outcomes prediction: serum creatinine, sex, hypertension and treatment. Hypertensive patients had, on average, an increase in 0.588 in mRS (p = 0.022), while treatment with microsurgery had a decrease in 0.555 (p = 0.038).

Conclusion: Patients with higher GFR had better outcomes after 6 months. Patients with higher GFR had better outcomes after 6 months. Creatinine presented an indirect role in GFR values and should be included in models for outcome prediction.

Key words: Creatinine. Intracranial Aneurysm. Glomerular Filtration Rate.

Introduction

Subarachnoid hemorrhage (SAH) cases represent 3% of the causes of stroke, with high rates of mortality and morbidity. The main cause of spontaneous SAH is the rupture of saccular aneurysms, known as aneurysmal subarachnoid hemorrhage (aSAH). Other less prevalent causes are arteriovenous malformations, fistulas, vasculitis, intracranial arterial dissections and drugs.

Creatinine is known for its role as a marker of renal function, but it is also related to several other factors, including nutritional status and a biomarker in several pathological processes as an indicator of severity or prognosis. Studies of neurological diseases show a clear correlation between creatinine levels and disease progression, including spinal muscular atrophy, spinal and bulbar muscle atrophy, Duchenne and Becker muscular dystrophy and acute encephalopathy. Studies in the field of cardiology have also shown the importance of this biomarker in cardiogenic shock, heart failure and cardiothoracic surgery. Finally, this association has also been demonstrated in other areas, such as oncology, gynecology and gastrointestinal.

Thus, the present study aims to evaluate the relationship between serum creatinine, glomerular filtration rate (GFR) and long-term outcome after treatment of intracranial aneurysm.
Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

**Methods**

**Ethical standards**

This research project was approved by the Ethics and Research Committee of the Hospital das Clinicas of FMUSP. Online registration CAPPesq: 15226 approved 06/20/2016. Approved on the Brazil platform CAAE number: 61719416.6.0000.0068. Patient consent was obtained for all participants.

**Study design**

This is a prospective cohort study with patients who were admitted in the hospital due to SAH, between January 2018 and November 2019. Social and demographic data from charts of patients from database from the Department of Neurosurgery of the Hospital das Clinicas (HCFMUSP) were collected. Serum creatinine and aneurysm intracranial rupture status upon admission and the modified Rankin scale (mRS) at 6 months were also obtained.

**Population data**

During this period, 401 patients (adult men and women) were admitted with intracranial aneurysm diagnosis at Hospital das Clinicas da FMUSP (HCFMUSP) Department of Neurological Surgery. From those 401 patients, 147 were included in this study (Fig. 1).

![Figure 1 - Population data and selection process based on inclusion and exclusion criteria; 147 patients were included in this study.](image)

Patients underwent clinical evaluation, which comprised age, sex and race. A questionnaire concerning previous risk factors to aneurysmatic disease was performed, including hypertension, diabetes mellitus, smoking, alcoholism, drug abuse, family history, previous SAH and time from the last event.

Besides that, a socioeconomic evaluation of the participants was performed, assessing scholarship, family income, occupation, and marital status. Based on clinical and imaging conditions, patients were treated with embolization or microsurgery.

Serum creatinine was obtained at admission and patients were followed for 6 months. At the end of the study, mRS was used to measure outcome after SAH.

**Exclusion criteria**

Patients without serum creatinine data upon admission or loss of follow up in less than 6 months.

**Inclusion criteria**

Patients of both gender and ages, with ruptured and unruptured brain aneurysm who were admitted to the HCFMUSP between January 2018 and November 2019 were included.
Statistical analysis

Linear and logistic regressions with serum creatine were used as independent and continuous variable. The outcome was quantified by mRS at 6 months. Significance level was established as 0.05. For the logistic regression, unfavorable outcome was defined as mRS > 2.

Cutoff values for GFR were calculated based on receiver operating characteristic (ROC) curves, maximizing the metric function to determine the optimal cut point.

The variable selection method used was stepwise approach. The variables analyzed were serum creatinine, GFR, age, history of previous SAH, gender, age, smoking, alcoholism, aneurysm treatment (embolization or microsurgery) and aneurysm rupture. As unruptured aneurysms were included, Hunt Hess was not considered in the model. Predictor variables were either dropped or added to the logistic regression based on Akaike information criterion. The variables chosen were included in a separate linear regression model (Table 1, model 3).

Table 1 - Linear regression model for prediction of outcome 6 months after intracranial aneurysm event.

| Variables             | Model 1        | Model 2       | Model 3         | Model 4         |
|-----------------------|----------------|---------------|-----------------|-----------------|
|                       | Ruptured       | Unruptured    |                 |                 |
|                       | Estimate       | p-value       | Estimate        | p-value         |
| Intercept             | 3.058          | -             | 2.628           | -               |
| Serum creatinine      | 0.039          | 0.563         | –0.203          | 0.442           |
|                       | Model 2        |               |                 |                 |
| Coefficients:         | Estimate       | p-value       |                 |                 |
| Intercept             | 1.076          | -             |                 |                 |
| GFR (> 72.5 mL·min⁻¹) | –1.115         | 0.006*        |                 |                 |
| Aneurysm rupture      | 1.084          | 0.014*        |                 |                 |
|                       | Model 3        |               |                 |                 |
| Coefficients:         | Estimate       | p-value       |                 |                 |
| Intercept             | 1.331          | -             |                 |                 |
| Serum creatinine      | 0.052          | 0.146         |                 |                 |
| Gender (female)       | 0.429          | 0.085         |                 |                 |
| Hypertension          | 0.588          | 0.022*        |                 |                 |
| Treatment (microsurgery) | –0.555        | 0.038*        |                 |                 |
|                       | Model 4        |               |                 |                 |
| Coefficients:         | Estimate       | p-value       |                 |                 |
| Intercept             | 0.415          | -             |                 |                 |
| Serum creatinine      | 0.058          | 0.180         |                 |                 |
| GFR                   | 0.002          | 0.762         |                 |                 |
| Smoking               | 0.345          | 0.149         |                 |                 |
| Alcoholism            | –0.284         | 0.339         |                 |                 |
| Gender(female)        | 0.372          | 0.160         |                 |                 |
| Hypertension          | 0.523          | 0.050*        |                 |                 |
| Age                   | 0.011          | 0.237         |                 |                 |
| Aneurysm Rupture      | 0.191          | 0.492         |                 |                 |
| Treatment (microsurgery) | –0.579        | 0.036*        |                 |                 |

Model 1: Simple linear regression with serum creatinine as independent variable. Model 2: Logistic regression with GFR and aneurysm rupture as independent variables. Model 3: Multiple linear regression (stepwise) with serum creatinine, sex, hypertension and treatment as independent variables. Model 4: Multiple linear regression (stepwise) with serum creatinine, GFR, smoking, alcoholism, sex, hypertension, age, aneurysm rupture and treatment as independent variables.

Patients were also divided in ruptured and unruptured aneurysm groups. Serum creatinine was analyzed with Welch two sample t-test. The mRS – 6 months was analyzed with Fisher’s exact test for count data. A significance level of 0.05 was used.

The analyses were performed using the statistical software RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA.
Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

- **Results**

  **Epidemiology and comorbidity**

  Among the 147 patients included in the study, the average age was 57.06 ± 12.70 years, and 74.2% were female. Hypertension was present in 73.3% of the patients, 37.1% had previous diabetes mellitus, 49.5% were smokers, 20.0% were heavy alcohol drinkers, 14.2% have had SAH previously and 78.2% patients had ruptured aneurysm. Figure 2 shows the distribution of aneurysm rupture and mRS score after 6 months; 73.3% of patients were treated with microsurgery and the others with embolization. The median for the Glasgow coma scale (GCS) at admission was 14. (Table 2).

  **Figure 2** - Distribution of ruptured and unruptured aneurysm based on RANKIN – 6 months.

  **Table 2** - Patients' characteristics. Patients were divided in ruptured and unruptured aneurysm. p-value shows comparison between groups.

| Intracranial Aneurysm | Ruptured (115) | Unruptured (32) | p-value |
|------------------------|----------------|-----------------|---------|
| **Epidemiology**        |                |                 |         |
| Age (years)             | 56.76 (12.98)  | 58.15 (11.09)   | 0.548   |
| Gender (male)           | 82 (71.3%)     | 28 (87.5%)      | 0.068   |
| Hypertension            | 63 (78.8%)     | 14 (56.75%)     | 0.037*  |
| Diabetes mellitus       | 30 (37.5%)     | 9 (36.0%)       | 1.000   |
| Smoking                 | 45 (56.2%)     | 7 (28.0%)       | 0.021*  |
| Alcoholism              | 18 (22.5%)     | 3 (12.0%)       | 0.391   |
| Previous SAH            | 13 (16.2%)     | 2 (8.0%)        | 0.513   |
| Multiple aneurysm       | 16 (14.4%)     | 9 (90.0%)       | 0.000*  |
| **Clinical scales**     |                |                 |         |
| Hunt Hess – admission   | 2(1.22)        | -               |         |
| WFNS – admission        | 2 (1.61)       | -               |         |
| GCS – admission         | 14 (4.26)      | -               |         |
| Rankin – 6 months       | 3 (2.15)       | 1 (2.11)        | 0.105   |
| **Variables**           |                |                 |         |
| Treatment (microsurgery)| 75 (68.8%)     | 27 (90.0%)      | 0.020*  |
| GFR (mL-min⁻¹)          | 89.06 (25.28)  | 81.22 (25.58)   | 0.130   |
| Serum creatinine (mg-dL⁻¹)| 1.19 (3.01)   | 1.09 (1.46)     | 0.801   |

Data is presented as mean (SD) for continuous variables, median (SD) for ordinal variables and count (valid percentage) for categorical variables. SAH: subarachnoid hemorrhage; GCS: admission Glasgow coma scale; GFR: glomerular filtration rate (CKD-EPI).
Creatinine, GFR and aneurysm rupture

Serum creatinine was measured at hospital admission and was used to test whether it was correlated with aneurysm rupture. Mean serum creatinine in patients with unruptured aneurysm was 1.09, while patients with ruptured aneurysm had a mean creatinine of 1.18. This difference was not statistically significant (p > 0.05). Similarly, mean GFR was not significant different (p > 0.05) in patients with unruptured aneurysm was (81.22 mL min⁻¹) and ruptured aneurysm (89.06) (Table 2).

Creatinine and outcome

The median mRS at 6 months for all patients included in the study was 3. Linear regression analysis using serum creatinine as a predictor and the mRS at 6 months as outcome shows that serum creatine does not have a statistically significant influence (p > 0.05). Moreover, the subgroup analyses with ruptured and unruptured aneurysm shows no difference in neither group (p > 0.05). (Table 1, model 1). The linear regression with serum creatinine, aneurysm rupture and an interaction term (serum creatinine: aneurysm rupture) did not show any statistically significant variable.

Glomerular filtration rate and outcome

Glomerular filtration rate calculated by CKD-EPI was used to predict outcome measured by mRS at 6 months (Fig. 3). A ROC curve was used to determine the best cutoff point for GFR, 72.50 mL min⁻¹. Logistic regression using GFR and aneurysm rupture as dichotomous variable shows that both of them were significant. Patients with GFR < 72.50 had an OR of 3.049 [1.361–6.833] for worse mRS scores (p = 0.006). Similarly, aneurysm rupture had an OR of 2.957 [1.241–7.043] for worse mRS scores (p = 0.014) (Table 1).

Stepwise selection model and outcome

The selected variables based on the stepwise selection method were serum creatinine, sex, hypertension and method of treatment (microsurgery or embolization). The model with these variables is represented in Table 1, model 3. These four variables are considered important to build a model for outcome prediction. However, only hypertension (0.588 increase in mean mRS outcome, p = 0.022) and treatment (0.555 decreased mean mRS with microsurgery when compared to embolization, p = 0.038) were individually statistically significant predictors.

Model 4 (Table 1) uses variables significant in other models and the most common variables described in the literature as potential factor that can predict aneurysm outcomes. Hypertension and treatment (microsurgery) were statistically significant predictors (p = 0.050 and 0.036, respectively).
Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

Discussion

Symptoms of SAH include sudden severe headache that is usually associated with consciousness loss. It can cause secondary vasospasm, which may lead to cerebral ischemia, persistent headache, mental dullness and other severe conditions. Therefore, it is important to identify factors that can early predict aneurysms prior to rupture and, more importantly, predict the long-term outcomes of these patients.

Risk factors such as smoking, alcohol consumption, hypertension, female gender and age over 50 have been associated with increased chance of aneurysm rupture. This study findings corroborate the association between hypertension and smoking with the rupture of aneurysms causing SAH. Furthermore, those characteristics are not enough to precisely predict neither rupture of IA, nor prognosis of the disease. In these contexts, new biomarkers for intracranial aneurysm have been studied.

MPO, GM-CSF, MCP-1 and other cytokines are cited in numerous studies as potential biomarkers, because of its correlation with inflammation, especially with neutrophils and macrophages. Hostettler et al. found that procalcitonin on days 1, 3, and 7 could be used as prediction variable. The field of machine learning is quickly developing and trying to develop models to predict long term outcomes for intracranial aneurysm. Each study has a slightly different approach to select variables that might have an influence, with some of them being present almost invariably, including age, gender and clinical scales. The relatively small number of patients and absence of all variables available for the same population limits the precision for prediction for those studies.

Creatinine and GFR

Creatinine is an important biomarker in several diseases. This is most related with muscular denervation, because creatinine plays an important role in muscle fibers homeostasis. In muscular dystrophies and neurodegenerative disorders, for example, creatinine predicts the outcome because it measures the muscle mass. However, no relation with serum creatinine was found when studying Parkinson’s disease, mainly because it does not involve motor neurons.

When measuring serum creatinine, one is also indirectly assessing creatinine clearance and estimating GFR, which can be calculated from CKD-EPI, and this formula uses serum creatinine values and other variables, including age, gender and race to estimate the outcome of the patients. The correlation between GFR and cardiovascular diseases is already widely discussed in the literature, this relationship occurs because it predicts that the renal excretion is failing, thus increasing the cardiac output and therefore problems related to the cardiovascular system.

Huang et al. found that increased albuminuria was related to higher risk of stroke. The literature reveals that albuminuria is closely related to lower GFR, so one can conclude that lower GFR can be a risk factor for stroke. It is also associated with reduced ejection fraction, which increases the risk for several diseases, such as heart failure. Furthermore, GFR calculated by CKD-EPI is also an important risk factor for bleeding in patients with atrial fibrillation, and, because of that, it can predict the prognosis of these patients.

In this study, patients were divided using a GFR cutoff point of 72.50 (mL·min⁻¹). Higher GFR was correlated with lower 6 months Rankin scores. Those patients had an OR of 0.327 for unfavorable outcomes. As previously shown, it was found that ruptured aneurysm was associated with poor outcomes, with an OR of 2.957. The relatively small number of patients with unruptured aneurysm and high Rankin score might be responsible for the lack of statistical significance for creatinine. The study of the role of creatinine and GFR in the pathophysiology of the aneurysms and others biomarkers can also contribute to clarify this relation, but more research is needed in this field.

A model using stepwise approach that selected the best variables to predict a more precise outcome of the patients in 6 months was used. Although not all selected variables were significant, the method found that creatinine, sex, hypertension and treatment option are the most sensitive to predict the final result. The patients with elevated serum creatinine, presence of hypertension or female gender had higher Rankin scale values when evaluated after 6 months, showing a worsening in the prognosis. On other hand, the multiple linear regression suggests that patients undergoing microsurgery had lower mRS results when compared to patients undergoing embolization, suggesting a better prognosis.
Finally, a model with several variables that have already been described in the literature with a possible association with the outcome of patients with aneurysm was used, in which it was noticed that the GFR loses importance when being in the same model as serum creatinine, gender and age, probably because they are correlated through the formula that were used to calculate the GFR56. This model also confirmed the relevance of hypertension and the treatment choice, remaining statistically significant to predict more precisely the outcome based in the mRS of these patients in 6 months.

Future studies should try to elucidate the different mechanism involved in the pathophysiology of intracranial aneurysm, especially the molecular basis for other biomarkers. It is important to prevent and provide better treatment for intracranial aneurysm, but also understand why some patients have better long-term outcomes.

There are some limitations in this study, a clinical trial with randomization of treatment and a longitudinal control of serum creatinine levels is necessary for a clear answer. The inclusion of more variables in the prediction model would demand more patients.

## Conclusion

Models to predict aneurysm outcome are important to take medical decisions that will improve patient’s quality of life. This study shows that creatinine was not directly related to mRS 6 months outcome, but might have a role in predictions models as shown by the stepwise selection model approach. Furthermore, GFR can be used to help predict long term outcomes. Patients with GFR lower than 72.5 mL·min⁻¹ had an OR of 3.049 (p = 0.006) for worse outcome after 6 months measured by mRS.

## Authors’ contribution

Conception and design: Rabelo NN, Pipek LZ, Telles JPM and Nascimento RFV; Acquisition of data: Pipek LZ, Barbato NC, Coelho ACSS, Barbosa GB and Yoshikawa MH; Statistical analysis: Pipek LZ and Telles JPM; Manuscript preparation: Rabelo NN, Pipek LZ and Nascimento RFV; Critical revision: Rabelo NN, Pipek LZ, Teixeira MJ and Figueiredo EG.

## Data availability statement

All dataset were generated or analyzed in the current study.

## Funding

Not applicable.

## References

1. Etminan N, Chang HS, Hackenberg K, De Rooij NK, Vergouwen MDI, Rinkel GJE, Algra A. Worldwide incidence of aneurysmal subarachnoid hemorrhage according to region, time period, blood pressure and smoking prevalence in the population: a systematic review and meta-analysis. JAMA Neurol. 2019;76(5):588-97. https://doi.org/10.1001/jamaneurol.2019.0006

2. Rosa S, Samoni S, Ronco C. Creatinine-based definitions: from baseline creatinine to serum creatinine adjustment in intensive care. Crit Care. 2016;20:69. https://doi.org/10.1186/s13054-016-1218-4

3. Alves CRR, Zhang R, Johnstone AJ, Garner R, Nwe PH, Siranosian JJ, Swoboda KJ. Serum creatinine is a biomarker of progressive denervation in spinal muscular atrophy. Neurology. 2020;94(9):e921-e31. https://doi.org/10.1212/WNL.0000000000008762
Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

4. Hijikata Y, Katsuno M, Suzuki K, Hashizume A, Araki A, Yamada S, Inagaki T, Iida M, Noda S, Nakanishi H, Banno H, Mano T, Hirakawa A, Adachi H, Watanabe H, Yamamoto M, Sobue G. Impaired muscle uptake of creatine in spinal and bulbar muscular atrophy. Ann Clin Transl Neurol. 2016;3(7):537-46. https://doi.org/10.1002/acn3.324

5. Wang L, Chen M, He R, Sun Y, Yang J, Xiao L, Cao J, Zhang H, Zhang C. Serum Creatinine Distinguishes Duchenne Muscular Dystrophy from Becker Muscular Dystrophy in Patients Aged ≤3 Years: A Retrospective Study. Front Neurol. 2017;8:196. https://doi.org/10.3389/fneur.2017.00196

6. Fukuyama T, Yamauchi S, Amagasa S, Hattori Y, Sasaki T, Nakajima H, Takei Y, Okuno J, Misawa Y, Fueki N, Kitamura M, Matsu H, Inaba Y, Hirabayashi S. Early prognostic factors for acute encephalopathy with reduced subcortical diffusion. Brain Dev. 2018;40(8):707-13. https://doi.org/10.1016/j.braindev.2018.04.005

7. Fuernau G. Lactate and other biomarkers as treatment target in cardiogenic shock. Curr Opin Crit Care. 2019;25:403-9. https://doi.org/10.1097/MCC.0000000000000628

8. Kazory A, Ronco C. Are we barking up the wrong tree? Rise in serum creatinine and heart failure. Blood Purif. 2019;48(3):193-5. https://doi.org/10.1159/000500409

9. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, Schmidlin D. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: Do we have to revise current definitions of acute renal failure? Crit Care Med. 2008;36(4):1129-37. https://doi.org/10.1097/CCM.0b013e318169181a

10. Willegger M, Posch F, Schieder S, Funovics PT, Scharrer A, Brodowicz T, Ay C, Windhager R, Panotopoulos J. Serum creatinine and albumin predict sarcoma-specific survival in patients with myofibroblastic and fibroblastic sarcomas. J Orthop Res. 2017;35(12):2815-24. https://doi.org/10.1002/jor.23598

11. Panotopoulos J, Posch F, Funovics PT, Willegger M, Scharrer A, Lamm W, Brodowicz T, Windhager R, Ay C. Elevated serum creatinine and low albumin are associated with poor outcomes in patients with liposarcoma. J Orthop Res. 2014;34(3):533-8. https://doi.org/10.1002/jor.23002

12. Życzkowski M, Prokopowicz G, Taborowski P, Nowakowski K, Rajwa P, Stelmach P, Paradyż A. Basic Parameters of Blood Count, Serum Sodium and Creatinine as Prognostic Factors for Renal Cell Carcinoma at Five-Year Follow-Up. Med Sci Monit. 2018;24:3895-902. https://doi.org/10.12659/MSM.906867

13. Lafleur J, Hefler-Frischmuth K, Grimm C, Schwaines R, Gensthaler L, Reiser E, Hefler LA. Prognostic Value of Serum Creatinine Levels in Patients with Epithelial Ovarian Cancer. Anticancer Res. 2018;38(9):5127-30. https://doi.org/10.21873/anticanres.12834

14. Kamil Faiz FZ, Mehrabian S, Saad M, Aisenberg GM. Prognostic value of serum lipase levels in patients with small bowel obstruction. Baylor Univ Med Cent Proc. 2018;31(3):276-9. https://doi.org/10.1080/08998280.2018.1446637

15. Lankisch PG, Weber-Dany B, Maisonneuve P, Lowenfels AB. High Serum Creatinine in Acute Pancreatitis: A Marker for Pancreatic Necrosis? Am J Gastroenterol. 2010;105(5):1196-200. https://doi.org/10.1038/aig.2009.688

16. Macdonald RL, Schweizer TA. Spontaneous subarachnoid haemorrhage. Lancet. 2017;389(10069):655-66. https://doi.org/10.1016/S0140-6736(16)30668-7

17. Fisher CM, Kistler JP, Davis JM. Relation of Cerebral Vasospasm to Subarachnoid Hemorrhage Visualized by Computerized Tomographic Scanning. Neurosurgery. 1980;6(1):1-9. https://doi.org/10.1227/00006123-198001000-00001

18. Frontera JA, Claassen J, Schmidt JM, Wartenberg KE, Temes R, Connolly ES Jr, MacDonald RL, Mayer SA. Prediction of symptomatic vasospasm after subarachnoid hemorrhage: the modified fisher scale. Neurosurgery. 2006;59(1):21-7. https://doi.org/10.1227/00006123-200507000-00001

19. Petridis AK, Kamp MA, Cornelius JF, Beez T, Besoglu K, Turowski B, Steiger HJ. Aneurysmal Subarachnoid Hemorrhage-Diagnosis and Treatment. Dtsch Arztebl Int. 2017;114(13):226-35. https://doi.org/10.3238/arztebl.2017.0226

20. Rose MJ. Aneurysmal subarachnoid hemorrhage: an update on the medical complications and treatments strategies seen in these patients. Curr Opin Anaesthesiol. 2011;24(5):500-7. https://doi.org/10.1097/ACO.0b013e32834ad45b
21. van Gijn J, Kerr RS, Rinkel GJ. Subarachnoid haemorrhage. Lancet. 2007;369(9558):306-18. https://doi.org/10.1016/S0140-6736(06)60153-6
22. Kundra S, Mahendru V, Gupta V, Choudhary A. Principles of neuroanesthesia in aneurysmal subarachnoid hemorrhage. J Anaesthesiol Clin Pharmacol. 2014;30(3):328-37. https://doi.org/10.4103/0970-9185.137261
23. Bonita R. Cigarette smoking, hypertension and the risk of subarachnoid hemorrhage: a population-based case-control study. Stroke. 1986;17(5):831-5. https://doi.org/10.1161/01.STR.17.5.831
24. International Study of Unruptured Intracranial Aneurysms Investigators. Unruptured Intracranial Aneurysms — Risk of Rupture and Risks of Surgical Intervention. N Engl J Med. 1998;339(24):1725-33. https://doi.org/10.1056/NEJM199812103392401
25. Thompson BG, Brown RD, Amin-Hanjani S, Broderick JP, Cockroft KM, Connolly ES Jr, Duckwiler GR, Harris CC, Howard VJ, Johnston SC, Meyers PM, Molyneux A, Ogilvy CS, Ringer AJ, Torner J, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing and Council on Epidemiology and Prevention, American Heart Association, American Stroke Association, 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):2368-400. https://doi.org/10.1161/STR.000000000000070
26. Lindgren AE, Kurki MI, Riikhinen A, Koivisto T, Ronkainen A, Rinne J, Hernesniemi J, Eriksson JG, Jääskeläinen JE, von und zu Fraunberg M. Hypertension predisposes to the formation of saccular intracranial aneurysms in 467 unruptured and 1053 ruptured patients in Eastern Finland. Ann Med. 2014;46(3):169-76. https://doi.org/10.3109/07853890.2014.883168
27. Harrod CG, Batjer HH, Bendok BR. Deficiencies in estrogen-mediated regulation of cerebrovascular homeostasis may contribute to an increased risk of cerebral aneurysm pathogenesis and rupture in menopausal and postmenopausal women. Med Hypotheses. 2006;66(4):736-56. https://doi.org/10.1016/j.mehy.2005.09.051
28. 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):626-36. https://doi.org/10.1016/S1474-4422(11)70109-0
29. Menghini VV, Brown RD, Sicks JD, O’Fallon WM, Wiebers DO. Incidence and prevalence of intracranial aneurysms and hemorrhage in Olmsted County, Minnesota, 1965 to 1995. Neurology. 1998;51(2):405-11. https://doi.org/10.1212/WNL.51.2.405
30. Liu H-J, Zhou H, Lu D-L, Jiao Y-B, Chen S-F, Cheng J, Yao X-J, Ren J-Y, Li S-F, Liu W, Gao J-C, Yue Y, Xu J-X, Zhang P-N, Feng Y-G. Intracranial Mirror Aneurysm: Epidemiology, Rupture Risk, New Imaging, Controversies and Treatment Strategies. World Neurosurg. 2019;127:165-75. https://doi.org/10.1016/j.wneu.2019.03.275
31. Huang R, Chen X. Increased Spot Urine Albumin-to-Creatinine Ratio and Stroke Incidence: A Systematic Review and Meta-Analysis. J Stroke Cerebrovasc Dis. 2019;28(10):104260. https://doi.org/10.1016/j.jstrokecerebrovasdis.2019.06.018
32. Zhang H-F, Zhao M-G, Liang G-B, Song Z-Q, Li Z-Q. Expression of Pro-Inflammatory Cytokines and the Risk of Intracranial Aneurysm. Inflammation. 2013;36(6):1195-200. https://doi.org/10.1007/s10753-013-9655-6
33. Chalouhi N, Theofanis T, Starke RM, Zanaty M, Jabbour P, Dooley SA, Hasan D. Potential Role of Granulocyte–Monocyte Colony-Stimulating Factor in the Progression of Intracranial Aneurysms. DNA Cell Biol. 2015;34(1):78-81. https://doi.org/10.1089/dna.2014.2618
34. Gounis MJ, Vedantham S, Weaver JP, Puri AS, Brooks CS, Wahhloo AK, Bogdanov AA Jr. Myeloperoxidase in Human Intracranial Aneurysms: Preliminary Evidence. Stroke. 2014;45(5):1474-7. https://doi.org/10.1161/STROKEAHA.114.004956
35. Hussain S, Barbarite E, Chaudhry NS, Gupta K, Dellarole A, Peterson EC, Elhammady MS. Search for Biomarkers of Intracranial Aneurysms: A Systematic Review. World Neurosurg. 2015;84(5):1473-83. https://doi.org/10.1016/j.wneu.2015.06.034
36. Kao H-W, Lee K-W, Kuo C-L, Huang C-S, Tseng W-M, Liu C-S, Lin CP. Interleukin-6 as a Prognostic Biomarker in Ruptured Intracranial Aneurysms. PLoS One. 2015;10(7):e0132115. https://doi.org/10.1371/journal.pone.0132115
Could outcomes of intracranial aneurysms be better predict using serum creatinine and glomerular filtration rate?

37. Torres R, Mancha F, Bustamante A, Canhao P, Fragata I, Montaner J. Usefulness of TNFR1 as biomarker of intracranial aneurysm in patients with spontaneous subarachnoid hemorrhage. Futur Sci OA. 2019;6(1):FSO431. https://doi.org/10.2144/bsoa-2019-0090

38. Hostettler IC, Muroi C, Richter JK, Schmid J, Neidert MC, Seule M, Boss O, Pangalu A, Germans MR, Keller E. Decision tree analysis in subarachnoid hemorrhage: prediction of outcome parameters during the course of aneurysmal subarachnoid hemorrhage using decision tree analysis. J Neurosurg. 2018;129(6):1499-510. https://doi.org/10.3171/2017.7.JNS17677

39. Liu J, Xiong Y, Zhong M, Yang Y, Guo X, Tan X, Zhao B. Predicting Long-Term Outcomes After Poor-Grade Aneurysmal Subarachnoid Hemorrhage Using Decision Tree Modeling. Neurosurgery. 2020;87(3):523-9.

40. Zheng K, Zhong M, Zhao B, Chen S-Y, Tan X-X, Li Z-Q, Xiong Y, Duan C-Z. Poor-Grade Aneurysmal Subarachnoid Hemorrhage: Risk Factors Affecting Clinical Outcomes in Intracranial Aneurysm Patients in a Multi-Center Study. Front Neurol. 2019;10:123. https://doi.org/10.3389/fneur.2019.00123

41. van Donkelaar CE, Bakker NA, Birks J, Veeger NJGM, Metzemaekers JDM, Molyneux AJ, Groen RJM, van Dijk JMC. Prediction of Outcome After Aneurysmal Subarachnoid Hemorrhage: Development and Validation of the SAFIRE Grading Scale. Stroke. 2019;50(4):837-44. https://doi.org/10.1161/STROKEAHA.118.023902

42. Ironside N, Buell TJ, Chen CJ, Kumar JS, Paisan GM, Sokolowski JD, Liu KC, Ding D. High-Grade Aneurysmal Subarachnoid Hemorrhage: Predictors of Functional Outcome. World Neurosurg. 2019;125:e723-8. https://doi.org/10.1016/j.wneu.2019.01.162

43. Goldberg J, Schoeni D, Mordsini P, Z’Graggen W, Gralla J, Raabe A, Beck J, Fung C. Survival and Outcome After Poor-Grade Aneurysmal Hemorrhage in Elderly Patients. Stroke. 2018;49(12):2883-9. https://doi.org/10.1161/STROKEAHA.118.022869

44. Rubbert C, Patil KR, Besoglu K, Mathys C, May R, Kaschner MG, Sigl B, Teichert NA, Boos J, Turowski B, Caspers J. Prediction of outcome after aneurysmal subarachnoid haemorrhage using data from patient admission. Eur Radiol. 2018;28(12):4949-58. https://doi.org/10.1007/s00330-018-5505-0

45. Toledo P, Rios PM, Ledezma A, Sanchis A, Alen JF, Lagares A. Predicting the Outcome of Patients With Subarachnoid Hemorrhage Using Machine Learning Techniques. IEEE Trans Inf Technol Biomed. 2009;13(5):794-801. https://doi.org/10.1109/TITB.2009.2020434

46. Wallimann T, Tokarska-Schlattner M, Schlattner U. The creatine kinase system and pleiotropic effects of creatine. Amino Acids. 2011;40(5):1271-96. https://doi.org/10.1007/s00726-011-0877-3

47. Norris KC, Smoyer KE, Rolland C, Van Der Vaart J, Grubb EB. Albuminuria, serum creatinine and estimated glomerular filtration rate as predictors of cardio-renal outcomes in patients with type 2 diabetes mellitus and kidney disease: a systematic literature review. BMC Nephrol. 2018;19:36. https://doi.org/10.1186/s12882-018-0821-9

48. Levey AS, Becker C, Inker LA. Glomerular Filtration Rate and Albuminuria for Detection and Staging of Acute and Chronic Kidney Disease in Adults: A Systematic Review. J Am Med Assoc. 2015;313(8):837-46. https://doi.org/10.1001/jama.2015.0602

49. Coresh J, Levey AS. A combination of change in albuminuria and GFR as a surrogate end point for progression of CKD. Clin J Am Soc Nephrol. 2019;14(6):792-4. https://doi.org/10.2215/CJN.04160419

50. Boer RA, Nayor M, DeFilippi CR, Enserro D, Bhambhani V, Kizer JR, Blaha MJ, Brouwers FP, Cushman M, Lima JAC, Bahrami H, van der Harst P, Wang TJ, Gansevoort RT, Fox CS, Gaggin HK, Kop WJ, Liu K, Vasan RS, Psaty BM, Lee DS, Hillege HL, Bartz TM, Benjamin EJ, Chan C, Allison M, Gardin JM, Januzzi JL Jr, Shah SJ, Levy D, Herrington DM, Larson MG, van Gilst WH, Gottthiener JS, Bertoni AG, Ho JE. Association of Cardiovascular Biomarkers With Incident Heart Failure With Preserved and Reduced Ejection Fraction. JAMA Cardiol. 2018;3(3):215-24. https://doi.org/10.1001/jamacardio.2017.4987

51. Hijazi Z, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW, Ezekowitz MD, Held C, Hylek EM, Lopes RD, Siegbahn A, Yusuf S, Granger CB, Wallentin L; ARISTOTLE and RE-LY Investigators. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016;387(10035):2302-11. https://doi.org/10.1016/S0140-6736(16)00741-8
52. Konczalla J, Platz J, Schuss P, Vatter H, Seifert V, Güresir E. Non-aneurysmal non-traumatic subarachnoid hemorrhage: patient characteristics, clinical outcome and prognostic factors based on a single-center experience in 125 patients. BMC Neurol. 2014;14:140. https://doi.org/10.1186/1471-2377-14-140

53. Xiang J, Natarajan SK, Tremmel M, Ma D, Mocco J, Hopkins LN, Siddiqui AH, Levy EI, Meng H. Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. Stroke. 2011;42(1):144-52. https://doi.org/10.1161/STROKEAHA.110.592923

54. Li Y, Corriveau M, Aagaard-Kienitz B, Ahmed A, Niemann D. Differences in Pressure Within the Sac of Human Ruptured and Nonruptured Cerebral Aneurysms. Neurosurgery. 2019;84(6):1261-8. https://doi.org/10.1093/neuros/nyy182

55. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. J Neurosurg. 2008;108(5):1052-60. https://doi.org/10.3171/JNS/2008/108/5/1052

56. George JA, Gounden V. Novel glomerular filtration markers. Adv Clin Chem. 2019;88:91-119. https://doi.org/10.1016/bs.acc.2018.10.005