Epidemiological characteristics and causes of death after Aneurysmal Subarachnoid Hemorrhage – SAH

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ABSTRACT

This study analyzed the epidemiological characteristics and causes of deaths after SAH in patients admitted to a referral hospital in southern Brazil. A hospital database was used, comprising the years 2006-2018, composed of 148 patients. Cross-tabulations and Logistic Regression were performed to determine the odds of death of epidemiological characteristics. Ruptured aneurysms had a higher incidence in women, aged between 41 and 60 years. Headache is the predominant symptom in 95% patients. Hypertension (61%) and smoking (47%) are the prevalent risk factors. The age group with the highest frequency of deaths is 71 to 80 years old. The causes of death are: external ventricular shunt (34%), ischemic injury (9%), bleeding (7%), cerebral edema (8%), sepsis (28%) and pneumonia (24.3%). Knowing the risk factors and complications involved provide important insights that help in understanding their genesis, treatment and prevention.

Keywords: Cerebral aneurysms; Risk factors; Subarachnoid hemorrhage.

1. INTRODUCTION

Among brain ictus, subarachnoid hemorrhage-SAH of aneurysmatic origin is one of the biggest global public health problems. It has an annual incidence of 9.1 per 100,000 worldwide, with wide regional variations, affecting the working-age population. [1,2]

In Brazil, the exact epidemiology of SAH is unknown and publications are scarce, despite extensive research in this field. The large epidemiological studies that address cerebrovascular diseases are not very specific, leading to the imprecision of the occurrence of this type of hemorrhage in the country.[3-5]

The genesis of cerebral aneurysms is multicausal and can be divided into two groups: modifiable and non-modifiable factors.[6] Because of its character, it is not possible to act directly on some of the predictors, for example, genetic factors.

The incidence of SAH has decreased more slowly in the last decades (0.6% per year) when compared to stroke in general (2% per year), with a mortality rate of 12% before hospital admission and from 26% to 40%, in 30 days, after treatment.[7]

The most recent epidemiological studies have shown that, contrary to the traditional concept, the incidence of SAH increases with age, with a predominance in women; however, the greatest risk of death falls on men.[4,8]

As for the causes of death resulting from aneurysmal rupture, findings in the literature reveal that many of them are related to the patient's own condition, associated with advanced age, comorbidities and lifestyle.[9] Others to a low clinical degree in the initial assessment, complications during hospitalization and treatment of this ictus.[10] Therefore, the primary strategy is still prevention.

In this context, it is understood that due to the lack of regional data, this research will allow the establishment of new guidelines and the implementation of prevention programs for SAH in primary health in the municipality.

Thus, this study aimed to analyze the epidemiological characteristics and causes of deaths after SAH in patients admitted to a referral hospital in southern Brazil, from 2006 to 2018.

2. METHODOLOGY

This research is similar to a quantitative study, due to the numerical nature of the data and the statistical treatment given to the data; descriptive for describing the risk factors and causes of death after SAH; retrospective due to the period in which the data analysis is made (2006-2018); and documentary because it is data from secondary sources of a referral hospital in southern Brazil.

The population of patients diagnosed with SAH, after neuroimaging and evaluation by a neurologist, was 1,680 patients. In order to avoid bias in terms of regional characteristics that could influence the onset of SAH, only patients residing in a municipality, headquarter of the referral hospital, were selected.

The epidemiological characteristics evaluated were sex, age, aneurysm site, size, morphology, registered risk factors, clinical evolution scales and cause of death.

To analyze the data, cross tabulations were made with absolute and relative frequencies; and logistic regression to determine the odds ratio of epidemiological characteristics for death. The analyses were performed using the statistical software SPSS (Statistical Package for Social Sciences) version 22.

As for ethical aspects, the study was submitted to the Research Ethics Committee (CEP) of the Regional University of Blumenau - FURB, under protocol 14903519.0.0000.5370.

3. RESULTS

The sample consisted of 148 patients, with a confirmed diagnosis of subarachnoid hemorrhage by ruptured aneurysm. Of these, 96 are women (65%) and 52 men (35%), with a mean age of 53.7 years.

Of the 148 patients affected by subarachnoid hemorrhage, 109 had results considered favorable (73.6%) and 39 patients (26.4%) died. Demographic data and risk factors are listed in Table 1.

In this table, although there is a higher incidence of SAH in women, the chances of death do not seem to be different between men and women, since the statistical difference was not significant (*p*-value = 0.907). Regarding the age group, in patients between 41 and 50 old, the chances of death are reduced (OR = 0.377; *p*-value = 0.035) when compared to other ages. On the other hand, patients between 71 and 80 years old may be three times more likely to die (OR = 3.121; *p*-value = 0.042).

With regard to risk factors, systemic arterial hypertension and Smoking are the most prevalent, with a frequency of 61% and 47%, respectively, in the total of patients diagnosed with SAH. However, none of the isolated risk factors constituted predictors of death (*p*-value> 0.05).

Table 1. Descriptive analysis and odds ratio of demographic data and risk factors

		Death		**Non-death**		**OR**	**95% CI**		***p*-value**
		n	%	n	%		Inferior	Superior	
Gender	Male	14	35.95	38	34.9%	1.046	.488	2.246	.907
	Female	25	64.05%	71	65.1%	.955	.445	2.051	.907
Age group	from 21 to 30 years	2	5.1%	7	6.4%	.788	.157	3.964	.772
	from 31 to 40 years	4	10.3%	4	3.7%	3.000	.712	12.633	.134
	from 41 to 50 years	7	17.9%	40	36.7%	.377	.153	.934	.035
	from 51 to 60 years	10	25.6%	31	28.4%	.868	.378	1.991	.738
	from 61 to 70 years	8	20.5%	19	17.4%	1.222	.486	3.072	.669
	from 71 to 80 years	6	15.4%	6	5.5%	3.121	.942	10.338	.042
	from 81 to 90 years	2	5.1%	2	1.8%	2.892	.393	21.268	.297
Risk factors	Heart disease	2	5.1%	8	7.3%	.682	.139	3.362	.639
	Diabetes mellitus	3	7.7%	7	6.4%	1.214	.298	4.948	.786
	Dyslipidemia	7	17.9%	19	17.4%	1.036	.398	2.695	.942
	Illicit drugs	1	2.6%	1	0.9%	2.842	.173	46.567	.464
	Ethylism	4	10.3%	8	7.3%	1.443	.409	5.088	.569
	Arterial hypertension	27	69.2%	64	58.7%	1.582	.725	3.450	.249
	Polycystic Kidneys	0	0.0%	0	0.0%	-	-	-	-
	Smoking	18	46.2%	51	46.8%	.975	.468	2.030	.946

Source: Research data.

Table 2 lists the clinical characteristics at the patient's admission, in which headache was the most prevalent symptom in the records, found in 95% cases, followed by signs of vomiting (46%) and neck

stiffness (43%). There were also signs of a decrease in the level of consciousness, with sleepiness (41%), mental confusion (30%), syncope (37%) and torpor (12%).

These initial clinical manifestations were also analyzed for prediction of death. Headache was the most prevalent factor, but does not constitute a predictor of death (OR = 0.192; *p*-value = 0.029), that is, this factor is common for all patients, with no distinction between outcomes. Neck stiffness, on the other hand, is more common in patients with a better prognosis (OR = 0.415; *p*-value = 0.030).

In contrast, patients intubated in the emergency department (OR = 6.476; *p*-value = 0.000), who experience sleepiness (OR = 4.963; *p*-value = 0.000) and syncope (OR = 2.980; *p*-value = 0.004) are more likely to die.

For the evaluation of patients, the Hunt-Hess and Fisher scales were applied. On the Hunt-Hess scale, 44% patients were assessed on grade II; 29% on grade III; and 14% on grade IV. And on the Fisher scale, 18% were assessed on grade II, 30% on grade III and 51% on grade IV.

Patients classified in grade II of Hunt-Hess and Fisher scales are less likely to have poor results (OR = 0.339; *p*-value = 0.009; and OR = 0.182; *p*-value = 0.025; respectively). Patients classified in grade IV of Hunt-Hess and Fisher scales are at least three times more likely to die than patients on other grades (OR = 3.889; *p*-value = 0.005; and OR = 3.358; *p*-value = 0.003; respectively).

Table 2. Descriptive analysis and odds ratio of the initial manifestations and Hunt-Hess and Fisher scales.

		Death		**Non-death**		**OR**	**95% CI**		***p*-value**
		N	%	n	%		Lower	Upper	
Initial clinical manifestations	Headache	34	87.2%	106	97.2%	.192	.044	.848	.029
	Mental confusion	12	30.8%	33	30.3%	1.024	.463	2.263	.954
	Convulsive Crisis	4	10.3%	10	9.2%	1.131	.333	3.840	.843
	Intubation	12	30.8%	7	6.4%	6.476	2.326	18.034	.000
	Sleepiness	27	69.2%	34	31.2%	4.963	2.249	10.953	.000
	Neck stiffness	11	28.2%	53	48.6%	.415	.188	.917	.030
	Syncope	22	56.4%	33	30.3%	2.980	1.403	6.331	.004
	Torpor	8	20.5%	10	9.2%	2.555	.927	7.039	.070
	Vomiting	13	33.3%	55	50.5%	.491	.229	1.054	.068
Hunt-Hess scale	I	1	2.6%	7	6.4%	.383	.046	3.221	.377
	II	10	25.6%	55	50.5%	.339	.150	.762	.009
	III	12	30.8%	31	28.4%	1.118	.504	2.482	.783
	IV	11	28.2%	10	9.2%	3.889	1.499	10.093	.005
	V	5	12.8%	5	4.6%	3.059	.835	11.209	.092
Fisher scale	I	0	0.0%	1	0.9%	.000	.000		1.000
	II	2	5.1%	25	22.9%	.182	.041	.807	.025
	III	9	23.1%	35	32.1%	.634	.272	1.479	.292
	IV	28	71.8%	47	43.1%	3.358	1.518	7.427	.003

Source: Research data.

Regarding the location and size of the aneurysms, 79% were small (<10mm) and saccular morphology (97%). The most affected blood vessels were the anterior communicating artery-AcoA (27.7%), the posterior communicating artery-AcoP (23.6%) and the bifurcation of the middle cerebral artery-bACM (12.6%). Data on the location and size of the aneurysms are presented in Table 3.

Table 3. Location and size of the aneurysms

Vessels	Small (<10mm)	Large (10-20mm)	Giant (>20mm)	Total	%
AcoA	37	4	0	41	27.7
ACoP	29	6	0	35	23.6
bACM	15	2	1	18	12.6
AB	7	4	0	11	7.4
ACA-p	7	1	0	8	5.4
ACI-O	2	3	1	6	4.0
PICA	4	0	1	5	3.3
ACI-Coa	2	1	1	4	2.7
b-ACI	2	0	1	3	2.0
ACI-Hps	1	1	0	2	1.3
cv-ACI	1	1	0	2	1.3
ACI-Po	0	2	0	2	1.3
Others	10	1	0	11	7.4
Total	117	26	5	148	100%

ACoA: anterior communicating artery / ACoP: posterior communicating artery / bACM: bifurcation of the middle cerebral artery / AB: basilar artery / PICA: posterior inferior cerebellar artery / ACA-p: pericallosal anterior cerebral artery / ACI-O: internal carotid artery ophthalmic segment / ACI-Coa: internal carotid artery anterior choroidal segment / b- ACI: bifurcation of the internal carotid / ACI-HP: internal carotid artery hypophyseal segment / cv-ACI: internal carotid artery vertebral segment / ACI-Po: internal carotid artery paraophthalmic segment / Others: an affected vessel.

Source: Research data.

The neurological complications found with greater evidence among patients included vasospasm (46%), hydrocephalus (11%), rebleeding (7%), cerebral edema (8%) and ischemic injury (9%). There was also a need for external ventricular drainage-EVD, used in 34% patients.

Among the most frequent clinical complications recorded, fever (28%), pneumonia (24.3%), sepsis (9%) and hemodynamic instability (9%) stand out. This descriptive analysis is preented in Table 4.

Table 4. Neurological complications

		Death		Non-death		OR	95% CI		*p*-value
		n	%	n	%		Lower	Upper	
Neurological complications	Convulsive Crisis	3	7.7%	1	0.9%	9.000	.907	89.265	.061
	EVD	26	66.7%	24	22.0%	7.083	3.166	15.848	.000
	Cerebral Edema	7	17.9%	5	4.6%	4.550	1.351	15.321	.014
	Hydrocephalus	6	15.4%	10	9.2%	1.800	.608	5.333	.289
	Ischemic injury	9	23.1%	5	4.6%	6.240	1.944	20.030	.002
	Rebleeding	7	17.9%	4	3.7%	5.742	1.580	20.874	.008
	Vasospasm	20	51.3%	48	44.0%	1.338	.643	2.784	.437
	Decompressive craniectomy	5	12.8%	3	2.8%	5.196	1.180	22.885	.029
	Ventriculitis	0	0.0%	5	4.6%	0.000	.000		.999
Clinical complications	Fever	19	48.7%	22	20.2%	3.757	1.717	8.220	.001
	Hemodynamic instability	17	43.6%	0	0.0%	-	.000	-	.999
	Blood transfusion	7	17.9%	3	2.8%	7.729	1.889	31.630	.004
	Pneumonia	21	53.8%	15	13.7%	6.596	2.872	15.149	.000
	Sepsis	11	28.2%	2	1.8%	21.018	4.403	100.323	.000
	UTI	0	0.0%	11	10.1%	0.000	.000		.999
	Heart disease	3	7.7%	1	0.9%	9.000	.907	89.265	.061

OBS: EVD: External ventricular drainage; UTI: Urinary tract infection.

Source: Research data.

Relating the neurological complications to the chances of death, EVD (OR = 7.083; *p*-value = 0.000), cerebral edema (OR = 4.550; *p*-value = 0.014), ischemic injury (OR = 6.240; *p*-value = 0.002), rebleeding (OR = 5.742; *p*-value = 0.008) and decompressive craniectomy (OR = 5.196; *p*-value = 0.029) increase the chances of a poor prognosis.

The same analysis was performed for clinical complications, in which patients with fever (OR = 3.757; *p*-value = 0.001), undergoing blood transfusions (OR = 7.729, *p*-value = 0.004), pneumonia (OR = 6.596; *p*-value = 0.000) and sepsis (OR = 21.018, *p*-value = 0.000) are more likely to die.

Of the total number of patients admitted for treatment of SAH, 37.3% were admitted to a ward, 26.3% were admitted to the ICU and 36.4% patients in the two units (ICU and ward). The average length of hospital stay was 17 days.

Among the patients who did not survive, 36 were confirmed with brain death (92.3%) and for 18 patients a protocol for organ donation was opened (46.2%), however 13 were donors (72.2%).

4. DISCUSSION

In this study, the main sociodemographic and clinical characteristics, risk factors and complications occurred in 148 patients diagnosed with aneurysmal subarachnoid hemorrhage (SAH), residents in the municipality where a referral hospital is located, in southern Brazil.

The sociodemographic characteristics of the study sample are similar to other studies already described, since the highest occurrence is in women. [3,11,12] This ictus was present in 65% women, with 53% of them in the age range between 41 and 60 years old.

Published series on cerebral aneurysm warn that age is an important data to be considered, as they are rare in children and the incidence increases according to age in both sexes.[4,8] Thus, the same behavior is true in relation to aneurysmal subarachnoid hemorrhage, until at least the eighth decade.[13] This seems to support the theory of hormonal decline in menopause, contributing to the greater occurrence of this ictus among women as age increases.[14,15]

Although there is a higher frequency of SAH in middle-aged patients, the age group from 71 to 80 years old was the one with the highest risk of death, with three times more chance of death in relation to younger patients. Such an event can be derived from metabolic changes, greater cerebrovascular sensitivity, less tolerance to increases in intracranial pressure and a predisposition to neurological complications during the treatment of SAH. These characteristics justify the fact that the elderly generally have a worse prognosis than younger patients when affected by SAH.[16]

Among the risk factors, although arterial hypertension and smoking are the most present in patients diagnosed with SAH, in this study they were not predictors for deaths. These findings are consistent with previous studies.[17] However, the analysis was conducted in isolation and that although not associated with deaths, there is a possibility of mutual influence between the risk factors that can affect the result.[18]

Different authors agree on the synergistic effect of tobacco with high blood pressure on the risk of SAH. Correlated to the formation of the aneurysmal sac and to the induction of endothelial dysfunction in intracranial arteries, triggering an inflammatory process and, consequently, the appearance of the aneurysm and its rupture.[18-21]

In this research, 41% of the patients who died had SAH and were also smokers. It was also found that 51% of the patients who died had two to four comorbidities, 26% had only one and 23% had no comorbidity.

The most prevalent initial symptom described was headache, present in 95% patients, with distinct characteristics and intensity, being the main reason for seeking specialized care. This is supported by other studies where this symptom can reach up to 97% cases, among younger patients[22,23], accompanied or not by vomiting, with the duration of pain varying between one and two weeks.[24]

It was also observed that 12% patients reported experiencing headache between 3 and 12 days. Nevertheless, this symptom did not correlate with the increased chances of death, in line with the publications in the current literature.[25,26]

From the initial clinical manifestations, changes in the level of consciousness presented a greater risk of poor prognosis. Among those registered, sleepiness was present in 41% patients and syncope in 37% and had a greater relationship with death.

Lowering or loss of consciousness, mental confusion and numbness in the initial care of patients with SAH are an important indicator of brain injury. This injury is associated with worse grades on Hunt-Hesse and Fisher scales and affects approximately 25% to 53% of patients with SAH.[27]

In international studies,[9,10,27] as well as the results of this study, the change in the level of consciousness results in decreased cerebral perfusion, with a strong association with edema and cerebral ischemia, with unfavorable results.

In the initial assessment, 49% patients were classified in the Hunt-Hess grades I and II and 19% in the same grades as the Fisher scale. At these thresholds, headache was reported by 100of patients. Signs of vomiting and neck stiffness were also found in similar percentages among them, thus indicating milder symptoms, which suggests the patient ability to self-report. These symptoms were not predictive of death, being compatible with data found in the current literature.[12,25]

When analyzing patients classified as Hunt-Hess grade III (29% patients) and Fisher III (30% patients), this grade was also unrelated to deaths. Signs of change in the level of consciousness characteristic of this grade were present in patients with different outcomes and can significantly increase the risk of complications, such as vasospasm and ischemic injury.[27,28] It is therefore suggested that the change in the level of consciousness present in initial assessment implies a higher risk of severity in relation to milder cases.[10]

Patients who were on Hunt-Hess grades IV and V (21%) and Fisher grade IV (51%) had greater impairment and associated risk factors (arterial hypertension and smoking), greater association with neurological complications (cerebral edema, hydrocephalus, rebleeding, vasospasm, EVD-external ventricular drainage and decompressive craniectomy) and increased risk of death in relation to the other grades.

Studies on determinants of unfavorable outcome after SAH[12,28,29] describe that the higher grades of the scales (Hunt-Hess and Fisher) are associated with multiple causes, such as the exact time of bleeding, associated risk factors, delay and imprecision in diagnosis and early neurological complications (convulsions, increased intracranial pressure and altered level of consciousness).

The morphological characteristics, size and location of the aneurysms, on the other hand, were not associated with poor outcomes when analyzed. Although the literature is abundant and with different results,[30-33] these characteristics were also not predictors of death.

Neurological complications after SAH are a reflection of causes underlying the clinical degree at admission and neuroimaging. The associated comorbidities, age and life habits of patients reflect the severity of signs and symptoms and the occurrence of events of greater or lesser severity during hospitalization and treatment.

This fact is portrayed in the literature[28,29,34,35] relating severe neurological events to a greater chance of death and worse grades (Hunt-Hess and Fisher) in the initial assessment of patients.

Among the complications, which are predictors of deaths, are EVD, ischemic injury, cerebral edema, rebleeding and decompressive craniectomy. Among these, it was found that patients with EVD are those most likely to die (OR = 7.083; CI = 3.1-15.8; p = 0.000).

As for vasospasm, diagnosed in 46% patients, it was present in different grades on Hunt-Hess and Fisher scales, with no statistical significance for death (OR = 1.338; p-value = 0.437). This can be justified by the

close relationship that this variable has with the initial clinical status and by the amount of bleeding revealed on the Fisher scale.[12]

In addition to the effects of neurological complications, patients are also predisposed to clinical complications that impact their prognosis, such as fever of infectious origin and nosocomial infections.

Fever was present in 28% patients, characterized as a temperature> 38.2 ºC, with administration of antibiotics for treatment, associated with complications such as pneumonia, sepsis, urinary tract infection, EVD and, although not described in this study, there are possibility of infections due to the use of central and peripheral catheters, which are not uncommon in these cases.

Both fever and infectious complications are considered predictors of poor results, associated with a greater number of days of hospitalization[36], with this symptom being identified on the fifth day after hospitalization for SAH.[37]

Of the patients who presented with fever, 48.7% of the patients who died (OR = 3.757; *p*-value = 0.001), with the first episode in 4-5 days hospitalization. Similar to previous results described[36-38], in which this symptom was associated with infection in 47%, predicting poor results in patients with SAH.[38]

As for infection, pneumonia was found in this sample, present in 36 patients (24.3%), and in 32 (91.4%) of them, it was associated with mechanical ventilation.

This association is related to different factors including prolonged intubation, tracheostomy, use of concomitant nasoenteral tube, with increased risk of aspiration pneumonia, reduced levels of consciousness and immobility in bed.[39]

Another important factor that negatively influenced survival was sepsis, diagnosed in 9% hospitalized patients, and was correlated with low clinical grade on admission, reduced level of consciousness, intubation in the emergency department, mechanical ventilation, EVD and average length of stay in the ICU of 11 days. There was no association between this variable with the age of the patients. These findings, therefore, are compatible with the mortality rate from sepsis involving patients with SAH.[40]

Non-neurological complications are a real clinical challenge in patients with SAH. Hemodynamic instability appears as fluctuations in systemic blood pressure, with a tendency to hypotension and the need to use vasoactive drugs during ICU stay. Hemodynamic instability events were recorded in 43.6% patients in this study, who died.

As well as the need for blood transfusion recorded in 7% patients, which was also a risk factor for poor results, with an increase of almost eight times the chances of death in patients.

The literature shows that in order to maintain adequate cerebral perfusion in tissues at risk of ischemia, the oxygen supply through red blood cell transfusion is greater with increased hemoglobin concentrations and theoretically prevents a metabolic crisis.[41] However, this procedure is a subject of debate because blood transfusion is a risk factor for poor results in a patient with SAH.[42]

5. CONCLUSION

In this research, women were most affected by aneurysms and, according to the literature, this may be related to hormonal factors (decreased estrogen). Although risk factors, smoking and hypertension were

more prevalent, they did not present risks of death when evaluated in isolated ways, however, the synergy between them becomes a predictor of poor results.

As for headache, this was the most evident symptom among men and women. However, attention is drawn to the need to investigate this symptom of sudden onset and strong intensity, especially among women, since they have more headache (primary headache) compared to men and, sometimes, fail to perceive the difference in the intensity or pattern of pain and the diagnosis can be delayed.

The numerous complications during treatment and hospitalization are reflections of causes underlying the clinical condition when the patient seeks specialized care, that is, the associated comorbidities, age and life habits are correlated to the severity of signs and symptoms and occurrences of events with greater or lesser severity and a poor prognosis.

Thus, guidance campaigns are suggested that can be developed so that individuals with constant headaches seek specialized care to minimize the chances of aneurysm and hemorrhage with severe outcomes. Likewise, campaigns to combat environmental risk factors can be intensified.

Finally, some limitations of this study must be pointed out. First, it is a retrospective study of a single center, despite being a referral center in the region for the treatment of aneurysms. The analyses were carried out using secondary data, with information provided by the hospital. Thus, the records were not created specifically for this study.

Data were available in a dichotomous way, that is, there was information on whether or not the patient had a characteristic, without presenting absolute values referring to it, limiting the explanatory power of the phenomenon under study.

Positive points of the study comprise more regionally specific data and their behavior over a decade, which can assist in specific projects for the municipality, such as campaigns that promote healthier lifestyles, in order to minimize the occurrence of aneurysm and to assist in the women health program.

Future studies should analyze absolute data from the scales for measuring patient characteristics to determine the maximum and minimum thresholds that relate to aneurysms and, consequently, deaths.

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