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Predictive models of epidemiological outcomes for patients with subarachnoid hemorrhage

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***Abstract*—** *Subarachnoid hemorrhage-SAH is considered a serious disease with a high potential for mortality and disability worldwide. This study aimed to evaluate the epidemiological outcomes in patients with SAH from 2006 to 2018 through a predictive equation, considering the following variables: risk factors, early manifestations, complementary needs, neurological and systemic complications. The subjects of this study were hospitalized patients with a proven diagnosis of SAH, evaluated by the Hunt-Hess and Fisher scales and classified by the modified Rankin scale (mRS). To reach this objective, binary logistic regression was applied, with risk factors as independent variables and epidemiological outcomes as dependent. A total of 148 patients were documented, 65% female and 35% male, with a mean age of 53.7 years. Heart disease was an important predictor for the severe disability outcome, the combination of sensory impairment and syncope explained cases of death by 75.7%. Among neurological complications, hydrocephalus and vasospasm explained the severe cases and ischemic injury and rebleeding explained the death. For systemic complications, hyperglycemia and aspiration pneumonia together represented predictors for severe cases and death events, which can be explained by the presence of sepsis and fever. There is a need to intensify health prevention programs for chronic diseases and women's health, as well as implement hospital assessment protocols.*

I. INTRODUCTION

Stroke is the second leading cause of death and one of the main causes of disability worldwide, affecting an economically active part of the population and resulting in significant socioeconomic burden [1]. Stroke can be ischemic or hemorrhagic. Among the non-traumatic hemorrhages, subarachnoid hemorrhage (SAH) is a type of hemorrhagic stroke, in which there is blood extravasation into the subarachnoid space, resulting from the rupture of a cerebral aneurysm in 80% cases, with a mortality rate of 35% within 30 days [2].

Intracranial aneurysms are defined as abnormal dilatations of cerebral arteries, which occur at the weakest spots along the blood vessel wall, as a result of the increase in hemodynamic pressure to which they are subjected, and

are classified according to their shape and etiology, most commonly distinguished between ruptured and unruptured aneurysms [3].

Ruptured aneurysms are the most frequent cause of SAH, with considerable variation in incidence worldwide and a high lethality rate of up to 50%, and only 20% to 35% cases show good functional evolution [4,5] due to complications and little information about their management when compared to ischemic stroke [6]. The etiology of the aneurysm is multifactorial, and the risk factors may be related to family and genetic history, clinical conditions associated with the aneurysm, morphological characteristics, advanced age, sex and modifiable risk factors [7].

Among the modifiable predictors with greater predisposition and that can increase the risk of SAH are those related to lifestyle, such as tobacco and alcohol use, in addition to controllable comorbidities, arterial hypertension, dyslipidemia and diabetes [8]. As for the causes of death resulting from aneurysm rupture, findings in the literature reveal that many of them are related to the patient's own condition, associated with advanced age and comorbidities [9]. When hospitalized, the cause of death is related to the low clinical score in the early assessment, complications during hospital stay and the treatment of this stroke [10].

Recent epidemiological studies have shown that, contrary to the traditional concept, the incidence of SAH increases with age and is predominant in women, however, men are at greater risk of death [11,12]. As for the prevalence of females, hypotheses have been raised relating the decrease in hormonal rate (estrogen) with inhibition of collagen formation, affecting the layers (intima, media and adventitia) of cerebral blood vessels (arteries), which may explain the greater incidence of aneurysm rupture in women [13].

Another factor raised as a possible cause of cerebral aneurysms is the anatomical alterations of cerebral arteries of the Circle of Willis between men and women. The internal diameter of arteries in women is smaller compared to men, which would lead to a greater risk of aneurysm formation in this group [14].

For patients who survive the initial crisis, morbidity is up to 50%. Depression is present in 28.1% cases, significantly related to functional impairment, unemployment and low quality of life. Cognitive deficits can develop in the long term in 27% to 46% of cases, as well as a high prevalence of sleep disturbances [15,16,17], with a mortality rate of 12% before hospital admission and 26% to 40% after treatment, within 30 days [18]. Therefore, the primary strategy is still prevention, given that the etiology of SAH is mainly environmental. However, the implementation of preventive measures in tertiary care are equally important, since some conditions causing mortality in this environment are still unknown. Thus, the development of accurate care and treatment protocols for patients with SAH in the hospital area is valuable.

In this context, this study aimed to evaluate the epidemiological outcomes in patients with SAH from 2006 to 2018, treated at a referral hospital in southern Brazil, through a predictive equation, based on risk factors, early clinical manifestations, complementary needs, neurological and systemic complications.

II. METHOD

Data collection was based on secondary data, provided by the hospital, made available through an electronic spreadsheet, without information that would allow the identification of patients, that is, through an electronic spreadsheet containing only the requested data, previously screened by the Information Technology System.

Thus, data were collected from patients for the years 2006 to 2018, totaling 1,680 patients. And after screening, we obtained 148 records of SAH, only residents in the municipality. To achieve the proposed objective, preliminary analyses were performed, such as the calculation of absolute and relative frequencies of demographic, clinical, neurological, evaluative, treatment, topographic and patient outcome variables. Afterwards, the prevalence of risk factors in different outcomes was evaluated, according to the modified Rankin scale. Thus, cross-tabulation and Mann-Whitney U test were used to check for differences in risk factors between outcomes. In this test, value slower than 0.05 for the p-value indicate a statistical difference.

Binary Logistic Regression was also applied; the demographic, clinical, neurological, evaluative, treatment, topographic variables were predictor variables and the death was the dependent variable. In this analysis, the Odds Ratio (OR) allowed to assess the odds ratio that death will occur given a particular predictor variable.

Finally, predictive equations were generated for epidemiological outcomes using binary logistic regression, in which the outcome studied was coded as "1" and the others as "0". This procedure was performed for all outcomes.

To facilitate the analysis and determine equations that could explain the epidemiological outcomes, the Rankin scale was pooled. In this way, instead of seven groups, four were generated. Patients who at the time of hospital discharge were classified as asymptomatic formed group 0 (Asymptomatic), those who presented symptoms without disability or mild disability made up group 1 (Mild Disability); moderate, moderate-severe and severe

disabilities formed group 2 (Severe Disability); and deaths, group 3 (Death).

In relation to risk factors, we sought to verify whether they present a gradual increase in the complexity of outcomes.

To prove this perception, binary logistic regression was applied, with risk factors as independent variables and epidemiological outcomes as the dependent variable. Data were arranged in tables and only significant variables were kept.

The base equation of logistic regression for predicting outcomes is as follows:

$$g\,(x) = \beta_0 + \beta_1 X_1 + \cdots \beta_n X_n$$

where:

$g(x)$ = epidemiological outcome function

β_0 = constant of the equation

β_1= coefficient/weight of the variable in the equation

X_1= independent or predictor variable

To calculate the probability of a certain epidemiological outcome occurring, the result of the equation is used in the following inverse function:

$$E\,(Y) = \frac{e^{g(x)}}{1 + e^{g(x)}}$$

where:

$E(Y)$ =Probability that the event will occur

e = Euler number with an approximate value of 2.71

The results were presented in tables and descriptive texts.

III. ANALYSIS AND DISCUSSION OF RESULTS

Initially, a lower prevalence of systemic arterial hypertension-SHT was evidenced in the group of asymptomatic patients, which suggests that patients without this comorbidity are 3.7 (OR = 3.771; CI = 1.706 – 8.336; p = 0.001) more likely of not having sequelae at discharge (Table 1).

Regarding severe outcomes, the presence of heart disease increased by 13 times (OR = 13.2; CI = 3.340 – 52.840; p = 0.000) the chances of a patient having moderate, moderate-severe or severe sequelae and in the cases of death, no comorbidity was found associated with this outcome, but it was identified that patients between 41 and 50 years of age are less likely to die (OR = 0.377; CI = 0.153 – 0.934; p = 0.035).

For the outcome of mild disability, it was not possible to generate a predictive equation since no risk factor was significant to discriminate this outcome. This is due to the fact that risk factors have a similar prevalence when comparing patients with mild disability with other outcomes (Table 1). The other risk factors were not discriminating for the complexity of outcomes.

In short, it is reinforced that risk factors are not good predictors of epidemiological outcomes, especially death; but that may suggest more severe outcomes in the presence of SAH and heart disease.

Table 1 – Risk Factors as predictors of epidemiological outcomes

								95% C.I.for EXP(B)		Classification power
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Asymptomatic	SHT	-1.327	.405	10.760	1	.001	3.771	1.706	8.336	76.4%
	Constant	-1.792	.300	35.773	1	.000	.167			
Milddisability	Constant	-.554	.171	10.538	1	.001	.574			0%
Severedisability	Heart disease	2.587	.704	13.485	1	.000	13.286	3.340	52.840	87.8%
	Constant	-2.181	.282	59.851	1	.000	.113			
Death	41-50years	-.975	.462	4.447	1	.035	.377	.153	.934	73.6%
	Constant	-.768	.214	12.907	1	.000	.464			

Note: S.E- Standard error; df-Degree of freedom; Sig-significance; Exp(B)-Odds Ratio.
Source: Analysis result

Regarding the early clinical manifestations of the patient at the time of admission to the emergency room, sensory impairment, torpor and syncope can determine, with limitations, the epidemiological outcomes.

According to Table 2, sensory impairment had a negative relationship with the asymptomatic group. This means that the presence of sensory impairment at the time of hospital admission reduces the chances of the patient

being discharged from the hospital without sequelae (OR = 0.218; CI = 0.084 – 0.556; p = 0.002).

Similarly, patients who were intubated in the emergency room are less likely to be asymptomatic at the time of hospital discharge, since it is the most important variable characterizing asymptomatic patients. In addition, a descriptive analysis indicated that all patients with this outcome were not intubated in the emergency room. In other words, intubation in the emergency room reduces the chances of patients leaving asymptomatic at hospital discharge by 100%.

As for mild disability, the presence of sensory impairment also decreased the chances of belonging to this outcome (OR = 0.458; CI = 0.225 – 0.933; p = 0.031). Comparing the outcomes, the prevalence of sensory impairment in the mild disability group was higher than in the asymptomatic group.

Severe outcomes were characterized by the occurrence of torpor upon hospital admission. This event increased by 4 times (OR = 4.143; CI = 1.344 – 12.774; p = 0.013) the chances of the patient having significant sequelae at discharge.

Patients who were admitted conscious were less likely to die (OR = 0.060; CI = 0.006 – 0.635; p = 0.019), but the presence of sensory impairment (OR = 4.305; CI = 1.869 – 9.914; p = 0.001) and syncope (OR = 2.267; CI = 0.992 – 5.177; p = 0.052) contributed to this outcome. It is noteworthy that syncope did not reach statistical significance (p>0.05), but was included in the model as the third most important variable. This condition indicates that syncope represented a predictor for the studied sample, but it may not be a predictor if tested in other samples.

In summary, patients without sensory impairment were more likely to have mild outcomes, and non-intubation may contribute to discharge without sequelae. Patients with torpor were more likely to have severe outcome, while sensory impairment and syncope were more favorable to death.

Table2 – Early clinical manifestations as predictors of epidemiological outcomes.

								95% C.I. para EXP(B)		Classification power
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Asymptomatic	ER Intubated	-19.619	9054.796	.000	1	.008	.000	.000	.	76.4%
	Sensoryrelegation	-1.232	.495	6.194	1	.013	.292	.111	.770	
	Constant	-.640	.229	7.778	1	.005	.527			
Milddisability	Sensoryrelegation	-.780	.363	4.627	1	.031	.458	.225	.933	63.5%
	Constant	-.254	.216	1.383	1	.240	.776			
Severedisability	Torpor	1.421	.574	6.121	1	.013	4.143	1.344	12.774	86.5%
	Constant	-2.115	.283	55.856	1	.000	.121			
Death	Sensoryrelegation	1.460	.426	11.761	1	.001	4.305	1.869	9.914	75.7%
	Syncope	.818	.421	3.770	1	.052	2.267	.992	5.177	
	Conscious	-2.806	1.200	5.466	1	.019	.060	.006	.635	
	Constant	.565	1.195	.223	1	.636	1.759			

Note: S.E- Standard error; df-Degree of freedom; Sig-significance; Exp(B)-Odds Ratio.
Source: Analysis result

With regard to neurological complications, there was a low prevalence of vasospasm in the asymptomatic group (OR = 0.302; CI = 0.129 – 0.706; p = 0.006) and absence of cerebral edema and hydrocephalus. According to Table 3, only vasospasm was significant, but the other two variables were selected as important since there were no cases of cerebral edema and hydrocephalus among asymptomatic patients. These results should be analyzed with caution, as they may be a characteristic of the study sample and not of the population of patients with SAH.

In the case of mild disability, low occurrence of rebleeding was a characteristic of this outcome. Patients who had rebleeding were less likely to be discharged without significant sequelae (OR = 0.158; CI = 0.020 – 1.274; p = 0.083).

For severe disabilities, patients with vasospasm (OR = 3.733; CI = 1.134 – 12.289; p = 0.030) and hydrocephalus (OR = 12.613; CI = 3.252 – 48.919; p = 0.000) were more likely to have this outcome.

In summary, asymptomatic patients with mild

disabilities were found to have no episodes of vasospasm, hydrocephalus, cerebral edema, and rebleeding. As for the severe outcomes, vasospasm and hydrocephalus were prevalent neurological complications. And in cases of death, rebleeding and ischemic injury seem to be determinant for this outcome.

Table 3 – Neurological complications as predictors of epidemiological outcomes

								95% C.I. for EXP(B)		Classification power
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Asymptomatic	Cerebral Edema	-20.157	11103.42	.000	1	.999	.000	.000	.	76.4%
	Hydrocephalus	-20.539	9765.012	.000	1	.998	.000	.000	.	
	Vasospasm	-1.197	.433	7.647	1	.006	.302	.129	.706	
	Constant	41.501	14786.53	.000	1	.998				
Milddisability	Rebleeding	-1.842	1.063	3.001	1	.043	.158	.020	1.274	63.5%
	Constant	1.382	1.106	1.561	1	.212	3.981			
Severedisability	Hydrocephalus	2.535	.692	13.434	1	.000	12.613	3.252	48.919	87.2%
	Vasospasm	1.317	.608	4.694	1	.030	3.733	1.134	12.289	
	Constant	-6.884	1.611	18.266	1	.000	.001			
Death	Ischemicinjury	1.929	.607	10.105	1	.001	6.885	2.095	22.624	77.7%
	Rebleeding	1.873	.675	7.704	1	.006	6.506	1.734	24.414	
	Constant	-5.234	1.074	23.750	1	.000	.005			

Note: S.E- Standard error; df-Degree of freedom; Sig-significance; Exp(B)-Odds Ratio.
Source: Analysis result

In relation to complementary needs, which refer to the use of materials and equipment that patients used during hospitalization, in the group of patients with asymptomatic outcomes (Table 4), there was a low prevalence of use of urinary catheter (UC). In other words, patients using UC had a low chance of being discharged without sequelae (OR = 0.035; CI = 0.010 – 0.124; p = 0.000). In addition, none of the patients with an asymptomatic outcome used Nasoenteral Tube (NET), tracheostomy, gastrostomy, mechanical ventilation or required intubation and decompressive craniectomy. However, they did not obtain statistical significance to explain the outcome.

In the group of patients with mild disabilities (Table 4), there was an occurrence of UC use, but less frequently than in groups with severe disability and death. Also in this group, most patients did not use mechanical ventilation. The use of mechanical ventilation reduced by 85.2% the chances of the patient being discharged without significant sequelae (OR = 0.148; CI = 0.053 – 0.412; p = 0.000).

Regarding patients with severe outcomes, the use of NET and tracheostomy were determinant for sequelae. Thus, the use of NET (OR = 5.913; CI = 1.201 – 29.113; p = 0.029) increased the chances of the patient having severe sequelae by almost six times, while tracheostomy (OR = 4.107; CI = 1.360 – 12.407; p = 0.012) increased this chance by four times.

Finally, for the cases of death, the use of NET and mechanical ventilation represented predictors for this outcome. It appears that NET increased the chances of death by 6.6 times, compared to those who did not use it (OR = 6.688; CI = 1.085 – 41.236; p = 0.041); and that mechanical ventilation increased this chance by 7.5 times (OR = 7.489; CI = 1.864 – 30.095; p = 0.005).

In general, patients who did not use UC and mechanical ventilation were likely to have asymptomatic outcomes and mild disability. The use of NET and tracheostomy can lead to severe outcomes. The criticality for death lies in the combination of the use of NET and mechanical ventilation.

Table 4 – Needs as predictors of epidemiological outcomes

								95% C.I. for EXP(B)		Classification power
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Asymptomatic	SV	-3.340	.640	27.271	1	.000	.035	.010	.124	77%
	Constant	3.372	.774	18.960	1	.000	29.125			
Milddisability	SV	1.041	.501	4.320	1	.038	2.832	1.061	7.561	68.2%
	Mechanicalventilat	-1.913	.523	13.361	1	.000	.148	.053	.412	
	Constant	.495	.604	.672	1	.412	1.640			
Severedisability	NET	1.777	.813	4.775	1	.029	5.913	1.201	29.113	86.5%
	Tracheostomy	1.413	.564	6.273	1	.012	4.107	1.360	12.407	
	Constant	-6.716	1.493	20.226	1	.000	.001			
Death	NET	1.900	.928	4.192	1	.041	6.688	1.085	41.236	76.4%
	Mechanicalventilation	2.013	.710	8.050	1	.005	7.489	1.864	30.095	
	Constant	-7.589	1.495	25.781	1	.000	.001			

Note: S.E- Standard error; df-Degree of freedom; Sig-significance; Exp(B)-Odds Ratio.
Source: Analysis result

Finally, when analyzing the clinical complications, in the asymptomatic group, fever may have a predictive power (Table 5), although less prevalent than in mild, severe outcomes and deaths. Thus, fever reduced the chances of a patient being discharged without sequelae (OR = 0.054; CI = 0.007 – 0.407; p = 0.005).

For patients with mild disability, the absence of pneumonia and the presence of polyuria seem to characterize this group. Patients with pneumonia were less likely to have mild disabilities (OR = 0.073; CI = 0.008 – 0.634; p = 0.018), while patients with polyuria were four times more likely to have this same outcome (OR = 4.034; CI = 1.137 – 14.316; p = 0.031).

Based on the records (Table 5), severe disabilities were marked by the presence of aspiration pneumonia and hyperglycemia. Aspiration pneumonia increased the chances of serious outcomes by 4 times (OR = 4.137; CI = 1.142 – 14.988; p = 0.031), a chance similar to patients with hyperglycemia (OR = 4.474; CI = 1.577 – 12.697; p = 0.005).

Finally, sepsis can increase the chances of death by 20.4 times (OR = 20.413; CI = 4.103 – 101.548; p = 0.000) and fever by 3.6 times (OR = 3.656; CI = 1.557 – 8.583; p = 0.000). It is noteworthy that all hypotensive patients with hemodynamic instability died.

In general, patients with asymptomatic outcomes did not present clinical complications. Those with mild disability had polyuria; the severe patients had aspiration pneumonia and hyperglycemia and the death cases had fever and sepsis.

Table 5 – Clinical complications as predictors of epidemiological outcomes

								95% C.I. for EXP(B)		Classification power
		B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper	
Asymptomatic	Fever	-2.925	1.033	8.009	1	.005	.054	.007	.407	76.4%
	Constant	-.764	.208	13.543	1	.000	.466			
Milddisability	Aspiration pneumonia	-2.624	1.106	5.625	1	.018	.073	.008	.634	
	Polyuria	1.395	.646	4.659	1	.031	4.034	1.137	14.316	65.5%
	Pneumonia	-1.535	.659	5.422	1	.020	.215	.059	.784	
	Constant	-.361	.200	3.262	1	.071	.697			
Severedisability	Hyperglicemia	1.498	.532	7.928	1	.005	4.474	1.577	12.697	85.8%
	Aspiration pneumonia	1.420	.657	4.675	1	.031	4.137	1.142	14.988	
	Constant	-2.840	.447	40.359	1	.000	.058			
Death	Fever	1.296	.435	8.865	1	.003	3.656	1.557	8.583	
	Sepsis	3.016	.819	13.577	1	.000	20.413	4.103	101.548	79.7%
	Constant	-1.769	.280	39.867	1	.000	.170			

Note: S.E- Standard error; df-Degree of freedom; Sig-significance; Exp(B)-Odds Ratio.
Source: Analysis result

With the information listed from the generation of predictive models by group of variables, it was possible to construct a summary box of the characteristics of each epidemiological outcome.

Table 6–Synthesis of clinical characteristics of epidemiological outcomes.

	Asymptomatic	**Milddisability**	**Severedisability**	**Death**
Risk factors	(-) SHT		(+) Heart disease	(-) 43 to 50 years
Early manifestations	(-) Sensoryrelegation (-) Intubation	(-) Sensoryrelegation	(+) Torpor	(-) Conscious (+) Syncope (+) Sensoryrelegation
Neurological complications	(-) Vasospasm (-) Hydrocephalus (-) Cerebral edema	(-) Rebleeding	(+) Hydrocephalus (+) Vasospasm	(+) Ischemicinjury (+) Rebleeding.
Needs	(-) UC	(+) UC (-) Mechanical ventilation	(+) NET (+) Tracheostomy	(+) NET (+) Mechanical ventilation
Clinical complications	(-) Fever	(-) Pneumonia (-) Aspiration pneumonia (+) Polyuria	(+) Hyperglicemia (+) Aspiration pneumonia	(+) Sepsis (+) Fever

(+) indicates the presence or higher prevalence and (-) indicates the absence or lower prevalence

IV. FINAL CONSIDERATION

The considerations of this study lie on two aspects: health development and promotion; and protocols in hospital care. For the first aspect, one must take into account the demographic data that are related to risk factors for aneurysm. Thus, it is suggested the development of prevention strategies and health education programs for greater adherence to the treatment of chronic diseases. And for the Municipal Health Department, to provide

sociodemographic data and risk factors characterizing patients with aneurysm in order to create prevention and screening strategies based on the phenotype raised.

For the second aspect, the development of proper care and treatment protocols for patients with SAH, as well as professional skills in the scope of tertiary care regarding the performance of screening, procedures and techniques.

With regard to the limitation of the present study, it is worth noting that data of this research come from medical records and the information collected such as risk factors, early manifestations, neurological and clinical complications, needs and outcomes were treated in a dichotomous way, which limits the possibilities of analysis and interpretations.

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