

Trends in the mortality of non-traumatic subarachnoid hemorrhage in Colombia: a 10-year analysis of a nationwide registry

Tendências na mortalidade relacionada a hemorragia subaracnóidea na Colômbia: análise de um registro nacional de 10 anos

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ABSTRACT

Objective: To assess trends in mortality from 1999 to 2008 resulting from non-traumatic subarachnoid hemorrhage (SAH) in the Colombian population. **Method:** This population-based study analyzed all deaths by assuming a Poisson model. **Results:** Subarachnoid hemorrhage-related deaths showed a statistically significant increase of 1.6% per year ($p < 0.001$). The age-standardized analysis demonstrated an increased mortality trend of 3.3% per year ($p < 0.001$) in people older than 70 years, but a decreased mortality trend in people younger than 50. It remained stable in patients 50-69 years old. **Conclusion:** The overall SAH-related mortality rate in Colombia has increased because increased mortality among the elderly has been counterbalanced by reduced mortality rates in younger age groups. These disparities may reflect epidemiologic transition, treatment inequities, or a less favorable comorbid profile.

Keywords: intracranial aneurysm, subarachnoid hemorrhage, morbidity, mortality.

RESUMO

Objetivo: Avaliar as tendências da mortalidade relacionada a hemorragia subaracnóidea não-traumática (HSA) entre 1999 e 2008, na Colômbia. **Método:** Foi realizado um estudo de base populacional, com base na análise das causas de morte, assumindo um modelo de Poisson. **Resultados:** A incidência de mortes relacionadas a SAH mostrou um aumento estatisticamente significativo de 1,6% ao ano ($p < 0,001$) para toda a população. A análise ajustada por idade demonstrou aumento da mortalidade de 3,3% ao ano ($p < 0,001$) em pessoas com mais de 70 anos de idade, diminuição em pessoas com menos de 50 anos de idade e estabilidade em pessoas com idade entre 50 e 69 anos. **Conclusão:** A taxa geral de mortalidade relacionada a SAH na Colômbia aumentou, porque o aumento da mortalidade entre os idosos foi maior que a redução nas taxas de mortalidade em grupos etários mais jovens. Estas disparidades podem refletir transição epidemiológica, as desigualdades de tratamento ou um perfil de comorbidades menos favorável.

Palavras-chave: aneurisma, hemorragia subaracnoidea, morbidade, mortalidade.

INTRODUCTION

Non-traumatic subarachnoid hemorrhage (SAH) is a devastating disease. In 85% of patients it is caused by ruptured intracranial aneurysms (IAs). The most frequent remaining causes of SAH are ruptured arteriovenous malformations, vasculitis,

arterial dissections, coagulopathies, or cocaine abuse^{1,2}. In recent decades there have been advances in medical, surgical, and interventional treatments. However, the morbidity and mortality associated with this disease remain high. This suggests that more efforts are needed to improve clinical management and public health strategies in the prevention of risk factors.

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The incidence of SAH varies according to age, geographic region, gender, and other risk factors^{3,4}. Between 1950 and 2005, the incidence decreased only slightly, by approximately 0.6% per year⁴. By contrast, in several reports the case fatality rate (CFR) varied widely. A multinational study by Nieukamp et al.³ showed a 17% decrease in the CFR (from approximately 65%) during a three-decade follow-up period in some countries; however, in other settings the fatality rates were stable or increased. These differences among studies may prevent the generalization of epidemiologic parameters from one area to another, thereby demonstrating a need for specific parameters for each region. An understanding of the epidemiology of SAH over time would enable better resource allocation, ensure the appropriate targeting of preventive public health measures, and allow assessment of the effectiveness of existing management strategies⁵.

Most published SAH-related epidemiologic studies exclude elderly and pediatric patients and do not analyze gender-specific differences in mortality⁶. In addition, developing countries lack adequate epidemiology estimates of SAH-related mortality.

Cause-specific SAH-related mortality has not been previously assessed in Colombia. Time trends and their relation to demographic variables remain to be evaluated. The present study aimed to assess trends in the mortality of non-traumatic SAH from 1999 to 2008 in an upper-middle developing country.

METHOD

This population-based study was designed to evaluate the trends of SAH-related mortality in Colombia from 1999 to 2008, based on the analysis of all deaths in the country during that time. Data were obtained from the Colombian national registry of deaths. The analysis was performed by using the database of death certificates gathered by the Colombian National Department of Statistics (Departamento Administrativo Nacional de Estadística [DANE]). The database collects all mortality statistics in Colombia and classifies deaths by cause in accordance with the *International Classification of Diseases, 10th Revision* (ICD-10) (World Health Organization, 2010 Edition). In this database, each person's age and gender are also collected.

For analysis, five SAH-related ICD-10 codes were selected and gathered from the database. The ICD-10 codes selected for analysis were I60.0 to I60.7, but the ICD-10 code (S06.6) for traumatic subarachnoid hemorrhage was excluded. Population data were drawn from the DANE 1999-2008 population estimates for the country.

Statistical analysis

The database was stored in a Microsoft Excel spreadsheet and analyzed by Stata software (Stata 11; StataCorp; College

Station, TX, USA). In all analyses, a *p* value less than 0.05 was assumed to be statistically significant.

The present analysis classified SAH-related deaths into distinct age groups. All non-adult deaths were grouped according to the World Health Organization definition (i.e., the person was less than 20 years old). Adult deaths in people 20-69 years old were analyzed by 10-year age groups. The elderly population (i.e., older than 70 years) was analyzed separately. Annual mortality rates per 100,000 people were calculated and compared for each gender and age group.

Continuous variables reported the mean \pm the standard deviation (SD) as a measure of dispersion. Two independent rates were compared to assess statistical significance. By assuming a Poisson model, the analyses were performed to assess statistically significant changes over time. In each age group, the β coefficients with their respective 95% confidence intervals (95% CI) were estimated for men and for women. Because the β -coefficients were too low, the percentage of change was presented as 100β . The formula used to calculate the percent change was $100(\exp\beta - 1)$, in which $\exp\beta$ equals the mortality rate ratio.

RESULTS

During the 10-year study period, 1,893,635 deaths were recorded in Colombia, with a crude death rate of 453.3 deaths per 100,000 people. The registered SAH-related deaths in the country totaled 17,272 deaths, which included 10,431 women (60.4%) and 6841 (39.6%) men. The mean age at death was significantly higher in women (62.1 ± 17.3 years) than in men (56.5 ± 18.9 years) ($p < 0.001$).

The registered SAH-related deaths corresponded to 0.91% of the nationwide crude mortality. The proportion of SAH-related deaths showed a statistically significant increase during the overall study period and was estimated at 1.6% per year (95% CI, 1.0%-2.1%; $p < 0.001$) (Table 1).

The overall SAH-related mortality during the study period was 3.9 deaths per 100,000 people and ranged from 3.9 to 4.4 deaths per 100,000 people. Mortality from SAH was 4.5 deaths in women per 100,000 people, compared to 3.3 deaths in men per 100,000 people ($p < 0.001$).

Mortality rates in men and women revealed significantly more deaths in males of 20-24 years old (95% CI; 0.91 per 100,000 people) than in females in the same age group (95% CI; 0.72 per 100,000 people; $p = 0.047$). However, this trend was not present in patients 25-40 years old. In age groups older than 40 years, women had significantly higher mortality rates than men (Table 2).

The SAH-related mortality rate was higher in women at 1.9% per year (95% CI, 1.2%-2.6%; $p < 0.001$) than in men at 1.1% per year (95% CI, 0.3%-2%; $p = 0.008$) (Table 3). The rate for the combined population was 1.4% per year (95% CI, 0.8%-1.9%; $p < 0.001$).

An age-standardized analysis demonstrated a statistically significant decrease in mortality among people younger than 50 years, whereas it remained broadly stable in people 50-69 years old. However, in people older than 70 years, mortality increased by 3.3% per year (95% CI, 2.2%-4.4%; $p < 0.001$). The Figure presents the age-standardized mortality trends for each gender.

Table 1. The percentage of crude mortality due to SAH, the overall death rate, and SAH-related mortality per 100,000 people over the study period.

Year	Deaths rate (per 100,000 people)	Mortality due to SAH	Mortality rate of SAH (per 100,000 people)
1999	460.72	0.84%	3.86
2000	463.92	0.86%	3.98
2001	468.12	0.82%	3.85
2002	464.22	0.83%	3.87
2003	458.32	0.96%	4.39
2004	445.26	0.93%	4.12
2005	440.46	0.99%	4.36
2006	443.81	0.97%	4.31
2007	440.45	0.98%	4.30
2008	416.78	1.03%	4.30

SAH: subarachnoid hemorrhage.

Table 2. Comparison of mortality rates (per 100,000 people), grouped by gender and age.

Age group (y)	Male	Female	p-value
<20	0.32	0.28	0.12
20-24	0.91	0.72	0.047*
25-29	1.28	1.11	0.185
30-34	1.60	1.57	0.898
35-39	2.38	2.69	0.099
40-44	3.62	4.53	<0.001*
45-49	5.76	8.08	<0.001*
50-54	8.02	10.78	<0.001*
55-59	10.14	13.06	<0.001*
60-64	12.16	17.79	<0.001*
65-69	15.53	25.14	<0.001*
70-74	19.53	32.05	<0.001*
75-79	22.61	36.36	<0.001*
>80	36.24	48.47	<0.001*

*Indicates a statistically significant difference.

Table 3. Trends in mortality rates, grouped by gender and age.

Age group	Male		Female	
	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
<40	-3.1% (-5% to -1.2%)	0.002	-2.4% (-4.3% to -0.5%)	0.014*
40-49	-3% (-5% to -0.9%)	0.004	-2.6% (-4.3% to -0.9%)	0.003*
50-59	-0.3% (-2.1% to 1.6%)	0.754	-0.5% (-2.1% to 1%)	0.495
60-69	-0.3% (-2.2% to 1.6%)	0.729	-0.1% (-1.5% to 1.4%)	0.920
≥70	3.6% (2% to 5.3%)	<0.001	3.2% (2% to 4.4%)	<0.001*
Total	1.1% (0.3% to 2%)	0.008	1.9% (1.2% to 2.6%)	<0.001*

CI: confidence interval.

*Indicates a statistically significant difference.

DISCUSSION

This assessment is the first population-based study to estimate SAH-related mortality and nationwide trends in a developing country.

The present study found that the nationwide SAH-related mortality rate in Colombia is similar to the rate reported by studies from other countries, such as the United States, Brazil, England, and New Zealand, in which the incidences of IA and SAH are close to the worldwide average^{2,7-9}. The mortality rate in Colombia was lower than that in countries such as Japan, South Korea, Finland, and northern Sweden. These countries report SAH incidences as high as 27 cases per 100,000 population per year, and mortality rates of 9.5 to 15 deaths per 100,000 population^{6,10,11}.

In most countries with SAH-related mortality assessments, deaths have been declining or have remained steady for decades, even in countries such as Finland^{12,13}, Japan¹⁴ and Sweden¹⁵, where the incidence of SAH is highly. However, the present study found an increase of 1.4% per year in the SAH-related mortality rate (95% CI, 0.8%-1.9%) throughout the study decade.

Specific causes of this increase remain to be explained; however, several hypotheses can be made. First, Colombia is a developing country that is experiencing a demographic and epidemiologic transition, and in which mortality due to chronic and non-communicable diseases is becoming more frequent¹⁶. This epidemiologic transition may be evidenced

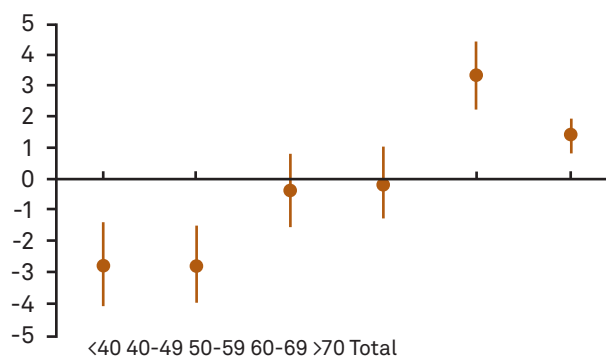


Figure. The percentage of annual change in the overall mortality of each age group.

by the percentage of overall SAH-related mortality, which increased by 18% over the study period. On the other hand, this trend in the mortality rate may reflect the quality of care offered to patients with SAH and the increased availability of diagnostic neuroimaging¹⁷.

In people over 70 years old mortality rates have increased significantly, which may be the result of poor performance status and comorbidities. By comparison, the mortality risk in people under 50 years old has diminished, and in people between 50 and 70 years old it has remained stable. The increased SAH-related mortality among the elderly has modified the trend in the overall population.

Gender differences in the mortality rates were observed in people 40 years of age. In females, the mortality rates were statistically higher after 40 years of age. This finding is consistent with several population-based studies that estimate an increased incidence and mortality in women, but predominantly after the menopause^{4,18}.

Most previous studies show a higher incidence of SAH after 50 years of age^{4,18-20}; however, in the present study the disparity in mortality rates was detected at a younger age and increased with age. In Colombian women, the mean age of menopause is between 47 and 53 years old²¹; therefore, this finding suggests that factors involved in the pathogenesis of IA and in inducing SAH begin just before the menopause rather than after, as was previously believed^{4,18}. This finding is interesting since the causes of the higher incidence of SAH in females remains unknown¹⁸, and since there is increasing evidence supporting the potential role of estrogens and progesterone in the pathogenesis of IA^{18,22}.

There is evidence from basic studies by Jamous et al.^{23,24} (using murine models) that showed a higher incidence of intracranial aneurysms in animals that did not receive treatment with 17 β -estradiol after oophorectomy. Aneurysms were even larger in this group than in rats administered exogenous estrogen^{23,24}. These observations suggest that estrogen therapy may prevent aneurysm formation after the natural menopause. This hypothesis is also supported by a case-control study that found an association between the non-use of hormone replacement therapy and intracranial aneurysms in women (odds ratio, 3.09; $p < 0.002$)²⁵.

The suppressive effect of estrogens on inflammatory cascades may be the reason that, up to the age of 40 years,

women are less likely to experience an SAH²². A large-scale blood profiling study of undiseased patients shows that young adult males generally have higher levels of circulating inflammatory proteins than females, who themselves have high levels of hormones²⁶. When these hormone levels are reduced, women are much more susceptible to an inflammatory response²⁷. This could potentially explain why male and female adults are more susceptible to SAH at different times in their lives. There is undoubtedly a multitude of genetic and environmental factors associated with aneurysm growth and rupture, although ruptured intracranial aneurysms have long been linked with inflammatory infiltration^{5,28}. Therefore, further research is needed to determine the role of sex hormones in the development and rupture of human saccular aneurysms, and to determine the effect of administering hormone replacement therapy before the clinical menopause (as some previous studies have proposed) to reduce the incidence and mortality associated with SAH in postmenopausal women²⁹.

This study has several limitations. Underreporting of deaths in the mortality database could affect the results, because patients with SAH were identified by using the diagnostic criteria of the ICD-10 codes and not from the patients' clinical information. The nature of this database could also have errors related to coding, documentation, and missing data³⁰. Another factor that may have affected the results of this study is information bias from the attending physician who prepared the report.

We conclude that, contrary to studies from other countries, the overall SAH-related mortality rate in Colombia increased by 1.4% per year from 1999 to 2008. The increased mortality among elderly patients counterbalanced the reduced mortality rates in the younger age groups. These disparities may reflect epidemiologic transition, treatment inequities, and/or a less favorable comorbid profile.

This study also provides evidence of higher mortality in females after the age of 40 years, which is earlier than the mean age of clinical menopause in this country. This finding and previous literature suggest that the depletion of sex hormones has a potential role in the formation of intracranial aneurysms before the menopause. Further research is needed to evaluate whether the administration of estrogens is effective as a preventive measure.

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