Spontaneous intracerebral hemorrhage in Mexico: results from a Multicenter Nationwide Hospital-based Registry on Cerebrovascular Disease (RENAMEVASC)

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Introduction. Scarce information exists on intracerebral hemorrhage (ICH) in Latin America, and the existent is derived from single-center registries with non-generalizable conclusions. The aim of this study is to describe the frequency, etiology, management and outcome of ICH in Mexico.

Patients and methods. We studied consecutive patients with ICH pertaining to the National Multicenter Registry on Cerebrovascular Disease (RENAMEVASC), conducted in 25 centers from 14 states of Mexico. The Intracerebral Hemorrhage Grading Scale (ICH-GS) at admission was used to assess prognosis at 30 days follow-up.

Results. Of 2,000 patients with acute cerebrovascular disease registered in RENAMEVASC, 564 (28%) had primary ICH (53% women; median age: 63 years; interquartile range: 50-75 years). Hypertension (70%), vascular malformations (7%) and amyloid angiopathy (4%) were the main etiologies. In 10% of cases etiology could not be determined. Main ICH locations were basal ganglia (50%), lobar (35%) and cerebellum (5%). Irruption into the ventricular system occurred in 43%. Median score of ICH-GS was 8 points: 49% had 5-7 points, 37% had 8-10 points and 15% had 11-13 points. The 30-day case fatality rate was 30%, and 31% presented severe disability. The 30-day survival was 92% for patients with ICH-GS 5-7 points, whereas it decreased to 27% in patients with ICH-GS 11-13 points.

Conclusions. In Mexico, ICH represents about a third of the forms of acute cerebrovascular disease, and the majority of patients present severe disability or death at 30 days of follow-up. Hypertension is the main cause; hence, control of this important cardiovascular risk factor should reduce the health burden of ICH.

Key words. Diagnosis. Epidemiology. Intracerebral hemorrhage. Outcome. Stroke.

Introduction

Intracerebral hemorrhage (ICH) is the spontaneous collection of blood within the brain parenchyma, caused by non-traumatic injury or aneurysmal rupture, whose shape, size and location are age and etiology dependent [1]. In Western series, ICH represent 5 to 19% of all cerebrovascular diseases (CVD), with a higher frequency among Hispanics, Asians and African Americans who live in those countries [2-6]. In Latin America, studies of hospital series of Ecuador, Mexico, Chile and Argentina reported a frequency of 23 to 40% [7-12]. In Chile, the PISCIS study done in the Iquique community, the ICH estimated incidence was 27.6/100,000 inhabitants [10]. In Mexico, the BASID hospital epidemiology surveillance recording showed a CVD incidence of 381.3 per 100,000, corresponding to a rate of 55/100,000 for ICH, ie, a frequency of 20.5% [11].

Despite its high prevalence, scarce information on ICH in our country has been mainly derived from stroke registries of a single center with its inherent conclusions bias [9-13]. This study analyzes the clinical spectrum, diagnosis, treatment and prognosis of ICH in Mexican patients included in a nation-wide multicenter hospital-based study.

Patients and methods

The Mexican National Registry of Cerebral Vascular Disease (RENAMEVASC) is a multi-hospital observational study, conducted from November 2002 to October 2004. It was designed by the Mexican Association of Cerebral Vascular Disease (AMEVASC) to improve CVD awareness in our country [14-16]. Briefly, investigators from 25 second and third level hospitals (14 states) included consecutive patients with acute stroke diagnosis that had at

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Accepted:
14.10.11.

How to cite this article:
Ruiz-Sandoval JL, Chiquete E, Gárate-Carrillo A, Ochoa-Guzmán A, Arauz A, León-Jiménez C, et al. Spontaneous intracerebral hemorrhage in Mexico: results from a Multicenter Nationwide Hospital-based Registry on Cerebrovascular Disease (RENAMEVASC). Rev Neurol 2011; 53: 705-12.

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least one computed tomography study (CT) that would classified the disease in either ischemic or hemorrhagic. Besides the neurological examination at hospital admission, all patients had a complete blood count and chemistry, liver function and coagulation tests. In selected cases, complementary studies were requested such as rheumatologic profile, magnetic resonance imaging (MRI) and cerebral angiography. Records from the database from patients that correspond to spontaneous ICH (n = 564) were also included for this study. We excluded patients with intra-parenchymal hemorrhage due to aneurysmal rupture, any traumatic causes, and those patients with a previously known cerebral vascular malformation (CVM), brain tumor or systemic cancer. In each patient, we also analyzed risk factors for ICH (including age, gender, hypertension, smoking, alcoholism, illicit drug use) according to established criteria [1]. Hypertension was regarded to patients with essential or secondary hypertension history with regular or irregular treatment, determination of systolic/diastolic blood pressure values equal or greater than 140/90 mmHg for more than two weeks after hospitalization, usually associated sites of ICH plus the following conditions: (1) high blood pressure on admission, (2) left ventricular hypertrophy documented by chest radiography and/or electrocardiogram, and (3) exclusion of other potential ICH causes [1,17,18].

At the emergency room, mean arterial pressure (MAP) and Glasgow Coma Scale (GCS) were recorded; MAP was considered to be the sum of one third of the difference between the systolic and diastolic blood pressure plus the diastolic blood pressure. Also, ICH location (lobar, ganglionic, cerebellar, brainstem or intraventricular), possible etiology (hypertensive, CVM, amyloid, coagulation disorders, drug use, undetermined), as well as any ventricular system aperture were recorded. The hematoma volume was calculated according to the $A \times B \times C / 2$ formula, where A = largest diameter, B = perpendicular diameter to A, C = number of sections (in cm) in which the hemorrhage appears in the CT scan [19]. Established treatment in the acute phase was classified as conservative (medical) and surgical (hematoma drainage, ventriculostomy or both). Functional outcome at hospital discharge and 30-days after ICH was based on the modified Rankin scale (mRS), where 0 = no symptoms, 1 = no significant disability, 2 = slight disability, 3 = moderate disability, 4 = moderately severe disability, 5 = severe disability, and 6 = death. We used the ICH grading scale (ICH-GS) [20] to estimate the one-month prognosis, according to the following rating system: Age < 45 years = 1 point, 45-64 years = 2 points, and ≥ 65 years = 3 points; 13-15 GCS at hospital admission = 1 point, 9-12 = 2 points, and 3-8 = 3 points; supratentorial hematoma location = 1 point, infratentorial location= 2 points; supratentorial hematoma volume < 40 mL = 1 point, 40-70 mL = 2 points, > 70 mL = 3 points; infratentorial hematoma volume <10 mL = 1 point, 10-20 ml = 2 points, > 20 mL = 3 points; no-ventricle hemorrhage extension = 1 point, ventricle extension = 2 points [20].

Statistical analysis

Demographic data is presented as simple relative frequencies. Quantitative normal distribution variables are expressed as mean and standard deviation (SD). Quantitative non-parametric variables distributions are expressed as medians and interquartile range (IQR). The Pearson χ^2 test was used (or Fisher's exact test when appropriate) to compare qualitative nominal variables frequencies between two groups, or to assess the homogeneity distribution of these variables into three or more groups. The Student t test was used to compare quantitative variables of normal distribution between two groups. Kaplan-Meier actuarial analysis were built to evaluate factors significantly associated with thirty-day death risk. These risk factors were first identified by an univariate analysis. All p values for comparisons and correlations were at two-tailed calculated and considered significant when p <0.05. The SPSS 17.0 was used in all calculations in this report.

Results

Of the 2000 acute stroke patients included in the RENAMEVASC study, 580 (29%) had a diagnosis of spontaneous ICH, being excluded 16 subjects due to aneurysmal rupture. Thus, we analyzed 564 (28.2%) patients with ICH: 299 (53%) females and 265 (47%) males (median age: 63 years, IQR: 50-75 years) (Table I). A total of 79 (14%) patients were younger than 40 years and 66 (12%) were over 80 years. Hypertension was the most common risk factor, with no difference between genders; however, it was significantly more frequent among those ≥ 65 years-old than younger subjects. Smoking and alcohol abuse were significantly more common among men than women. Most (41.7%) patients arrived at the hospital with a GCS of 13 to 15 points, but a significant amount (32.4%) of patients ≥ 65 years-old had a GCS < 8 points on their arrival, requiring mechanical ventilatory support (Table I).

Table I. Clinical condition at hospital admission, ICH topography and etiology, according to age and gender (*n* = 564).

	Total	Gender		*p*	Age group		*p*
		Female (*n* = 299)	Male (*n* = 265)		< 65 years (*n* = 298)	≥ 65 years (*n* = 266)	
Risk factors (%)							
Hypertension history	63.5	62.9	64.2	NS	59.1	68.4	0.021
Obesity	29.9	31.2	28.5	NS	31.4	28.3	NS
Smoking	23.8	13.8	35.2	< 0.001	24.9	22.6	NS
Alcoholism	18.9	5.4	34.1	< 0.001	20.9	16.6	NS
Diabetes mellitus history	17.7	18.4	17.0	NS	17.1	18.4	NS
Dyslipidemia history	9.1	8.7	9.5	NS	8.1	10.2	NS
Antiplatelets use	9.0	9.5	8.5	NS	5.8	12.5	0.006
Previous ICH	5.2	5.4	5.0	NS	6.1	4.1	NS
Glasgow Coma Scale (%)				NS			0.003
13-15	41.7	41.6	41.8		47.6	35.1	
9-12	31.6	31.4	31.8		30.8	32.4	
3-8	26.7	27.0	26.4		21.6	32.4	
Supratentorial location (%)							
Basal ganglia	50.4	44.8	56.6	0.005	47.3	53.8	NS
Lobar	35.1	39.1	30.6	0.033	35.9	34.2	NS
Intraventricular	4.1	4.7	3.4	NS	5.7	2.3	0.039
Infratentorial location (%)							
Brainstem	5.5	5.7	5.3	NS	6.7	4.1	NS
Cerebellum	4.8	5.7	3.8	NS	4.4	5.3	NS
Volume, mean (mL)	31.2 ± 32.0	30.2 ± 31.4	32.3 ± 32.7	NS	30.0 ± 30.5	32.4 ± 33.5	NS
Ventricular system irruption (%)	43.2	42.3	44.1	NS	40.1	46.6	NS
Etiology (%)				0.028			<0.001
Hypertensive	70.2	68.9	71.7		60.7	80.8	
Undetermined	9.8	11.7	7.5		14.1	4.9	
Cerebral vascular malformation	6.9	7.0	6.8		12.8	0.4	
Amyloid angiopathy	4.3	4.3	4.2		0.3	8.6	
Coagulopathy	3.9	2.7	5.3		6.0	1.5	
Miscellaneous	1.8	3.3	0		3.4	0	
Recreational drugs/sympathomimetics	1.4	0.7	2.3		2.0	0.8	
Anticoagulants/antiplatelets	1.2	1.0	1.5		0.7	1.9	
Tumors	0.5	0.3	0.8		0	1.1	

NS: not significant. Percentages may not sum up to 100 due to rounding.

Table II. ICH topography related to etiology.

	Supratentorial					Infratentorial			
	Lobar	Intraventricular	Basal ganglia			Brainstem			Cerebellum
			Putamen	Thalamus	Caudate	Midbrain	Pons	Medulla	
Hypertensive (%)	42.4	52.2	91.2	95.8	94.7	33.3	52.4	100.0	70.4
Undetermined (%)	2.0	8.7	5.4	3.4	0	11.1	23.8	0	11.1
Cerebral vascular malformations (%)	12.1	17.4	1.4	0.8	0	33.3	23.8	0	11.1
Amyloid angiopathy (%)	12.1	0	0	0	0	0	0	0	0
Coagulopathy (%)	8.6	4.3	0.7	0	0	11.1	9.5	0	0
Miscellaneous (%)	3.5	0	1.4	0	0	0	0	0	3.7
Recreational drugs/sympathomimetics (%)	2.5	0	0	0	5.3	11.1	4.8	0	0
Anticoagulants/antiplatelets (%)	2.0	8.7	0	0	0	0	0	0	3.7
Tumors (%)	1.5	0	0	0	0	0	0	0	0

Percentages may not sum up to 100 due to rounding.

The median (IQR) admission ICH-GS scale was 8 (7-9) points; 48.7% of patients with 5-7 points, 36.8% with 8-10 points and 14.6% with 11-13 points. There were no gender differences in the ICH-GS score.

The most common ICH location was deep supratentorial, mainly in basal ganglia, being more frequent among males than females (56.6% vs. 44.8%, respectively, p = 0.005). Except for primary intraventricular ICH, no significant differences regarding to age were observed in the hematoma location. Respecting the etiology, significant differences related to age and gender were observed, with a higher frequency of hypertensive and amyloid angiopathy causes in patients aged ≥ 65 years compared with those < 65 years (Table I). Differences respecting ICH etiology between genders were perhaps less relevant, except for a greater use of sympathomimetic drugs in males.

Table II shows the ICH location related to etiology. Hypertension appears as a cause for virtually any hematoma location, and as expected, CVM was more common in lobar, intraventricular and midbrain locations, while the amyloid angiopathy etiology had a lobar location only. Coagulopathies less frequently had a basal ganglia location, being most common in pons, midbrain or lobar, but it is noteworthy that ICH related to antiplatelets and anticoagulation drugs were more frequent in lobar, intraventricular and cerebellar location (Table II). The most common location for undetermined ICH etiology was the pons.

The hospital stay had a median of 9 days, with no differences by age or gender (Table III). Pneumonia and urosepsis were the most common in-hospital complications. Patients aged ≥ 65 years had pneumonia more frequently than their younger counterparts (35.3% vs. 23.6%, respectively, p = 0.002). Functional status at hospital discharge was generally unfavorable. Only 9.8% of the patients were discharged with minimal neurological deficit and the mortality rate was 28.4%, increasing to 29.6% to 30 days. Age ≥ 65 years was associated with poor prognosis, in this group there were more cases of death and severe functional impairment, both at discharge and at 30 days from the symptoms onset (Table III).

Notably, the association of hematoma volume and the probability of death at 30 days was related to ICH location (Fig. 1), so that the greater likelihood of death was observed for those with > 70 mL hematoma volume in the supratentorial space (61.8%) and > 20 mL in the infratentorial space (75%). This observation is supported by a thirty-day Kaplan-Meier actuarial survival analysis (Fig. 2) for volumes > 70 mL and > 20 mL, 40-70 mL and 10-20 mL

Table III. In-hospital evolution and 30-day functional outcome in ICH patients, according to gender and age (n = 564).

	Total	Gender		p	Age group		p
		Female (n = 299)	Male (n = 265)		< 65 years (n = 298)	≥ 65 years (n = 266)	
Hospital stay, median (IQR), days	9 (5-17)	9 (5-17)	9 (5-16.7)	NS	10 (6-17)	8 (5-17)	0.38
Surgical treatment (%)	9.5	9.5	9.5	NS	8.6	10.5	NS
In-hospital complications (%)							
Pneumonia	29.1	26.8	31.7	NS	23.6	35.3	0.002
Urosepsis	12.3	10.4	14.3	NS	10.4	14.3	NS
Arrhythmias	2.0	0.7	3.4	0.020	2.4	1.5	NS
Systemic venous thromboembolism	1.6	1.3	1.9	NS	1.3	1.9	NS
Modified Rankin scale at discharge (%)				NS			<0.001
0-1	9.8	9.7	9.8		14.1	4.9	
2-3	20.7	18.7	23.0		24.5	16.5	
4-5	41.1	46.2	35.5		37.9	44.7	
6	28.4	25.4	31.7		23.5	33.8	
Modified Rankin scale at 30 days follow-up (%)				NS			<0.001
0-1	12.1	11.4	12.8		16.8	6.8	
2-3	27.3	28.1	26.4		31.9	22.2	
4-5	31.0	33.4	28.3		27.5	35.0	
6	29.6	27.1	32.5		23.8	36.1	

IQR: interquartile range; NS: non significant. Percentages may not sum up to 100 due to rounding.

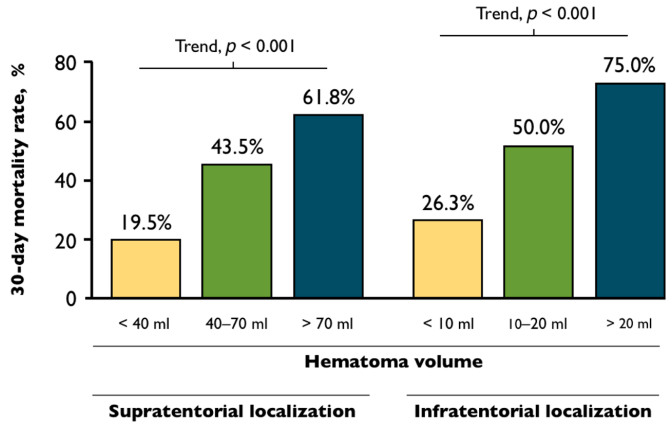
and < 40 mL and <10 mL, for supra and infratentorial spaces, respectively. Thus, age, GCS at admission, hematoma volume, location and ventricular irruption were significantly associated with death at 30 days, all included in the ICH-GS (Fig. 2). Patients with a ICH-GS score of 5 to 7 points showed a very low probability of death (8%), comparing with those with a score of 11 to 13 points, which only 27% survived at 30 days.

Discussion

In this Mexican multicenter study, we observed that ICH represents one third of all CVD types, being hypertension its main etiology. The hematoma location was strongly associated with its cause, confirming that early neuroimaging study plus medical history should orientate to an appropriate diagnosis and work-up approach. In addition to age, mortality risk factors were inherent to the acute hematoma characteristics.

These findings have fundamental importance in public health policy, considering that in Mexico, hypertension prevalence in the adult population (≥ 20 year-age) is 43% and half of these individuals are not aware of it, therefore, this population is excluded from effective treatment and preventive measures [21]. The latter could explain the high ICH frequency in Mexico, compared to countries like Spain and the United States [2-5]. However, unidentified ethnic differences, or suboptimal hypertension control could be associated with an increased ICH frequency in certain ethnic groups, as, for example, the hypertension frequency in countries like Spain does not differ significantly from Mexico [22-24], though the ICH relative frequency among the various forms of acute CVD is greater in this Latin

Figure 1. Thirty-day mortality in ICH patients, with respect to hematoma localization and volume.



American country. Moreover, the ICH frequency in some Latin American populations is getting closer to those in countries like Korea and China [25], which suggests a shared genetic background between Asians and Native Americans [26-28].

This study demonstrates the significant health burden that ICH represents for Mexico, it also shows that it is the second most common CVD type, and is associated with significant functional disability and death, since 60% of ICH patients at 30 days will have a significant functional dependence for daily living activities or will be dead. Therefore, an optimal hypertension and associated risk factors control is mandatory, since an inadequate control is a major risk factor not only for ICH, but also to ischemic stroke [29,30].

We notice that the ICH-GS components had an adequate performance, alone or together, in predicting the short-term ICH death tendency [20]. It also supports the importance of the hematoma volume location, because it is easier to deduce that the same hematoma volume in a smaller space, such as infratentorial, may cause a greater damage than in a larger space, such as supratentorial. However, this study was not designed to validate the ICH-GS, either to compare its performance with other well-known ICH prognostic scales [31-33].

This study has some limitations that should be noticed to avoid the generalization of its results. First, the RENAMEVASC study is a hospital registry based on consecutive patients, making it susceptible to health institutions participant selection bias. Furthermore, due to the clinical design and objectives of this registry, the follow-up period is short, precluding the assessment of the functional outcome of the ICH at medium and long term, which would allow to estimate the real impact of this disease. Nevertheless, this study provides important comparative data on epidemiology and enhances our clinical knowledge, showing that it is possible to predict since the hospital admission which patients would have a high probability of an adverse outcome, establishing important timely management decisions and closer relationship with the patient's family.

In conclusion, the ICH frequency in Mexico is high, which is comparable to other Latin American registries. The functional outcome of patients with ICH is poor in a significant cases proportion. Health governmental institutions should be involved for limiting the burden generated by arterial hypertension in Mexico.

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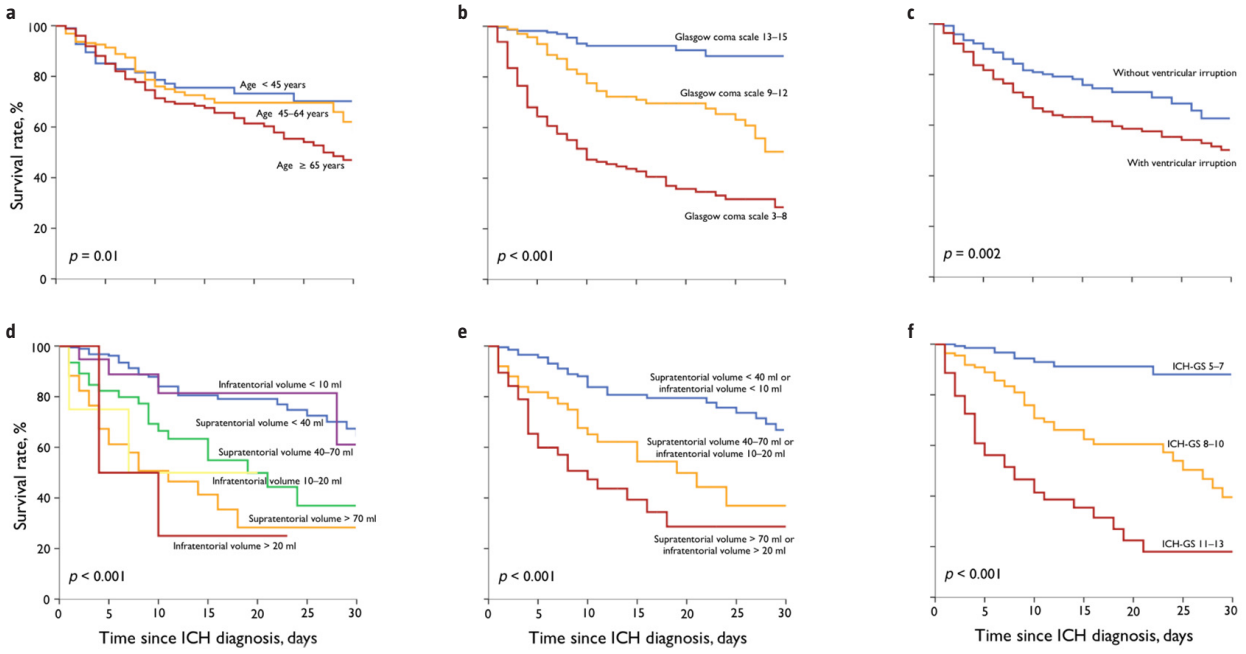
Figure 2. Kaplan-Meier curves showing 30-day survival after ICH as a function of age (a), Glasgow Coma Scale (b), irruption into the ventricular system (c), hematoma volume by intracranial localization (d), hematoma volume grouped according to ICH-GS scale (e), and ICH-GS scoring (f).



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Hemorragia intracerebral espontánea en México: resultados del Registro Hospitalario Multicéntrico Nacional en Enfermedad Vascular Cerebral (RENAMEVASC)

Introducción. Existe poca información respecto a la hemorragia intracerebral (HIC) en América Latina, y la existente ha sido derivada de registros hospitalarios de un solo centro con conclusiones no generalizables. El objetivo de este estudio es describir la frecuencia, etiología, manejo y desenlace clínico de la HIC en México.

Pacientes y métodos. Se estudiaron pacientes consecutivos con HIC incluidos en el Registro Nacional Mexicano de Enfermedad Vascular Cerebral (RENAMEVASC), conducido en 25 centros de 14 estados de la República Mexicana. Se usó la *Intracerebral Hemorrhage Grading Scale* (ICH-GS) para estimar el pronóstico a 30 días.

Resultados. De 2.000 pacientes con ictus agudo en el RENAMEVASC, 564 (28%) presentaron HIC espontánea (53% mujeres; edad media: 63 años; rango intercuartílico: 50-75 años). La hipertensión arterial (70%), las malformaciones vasculares (7%) y la angiopatía amiloidea (4%) fueron las causas más frecuentes. No se determinó la etiología en el 10% de los casos. Las localizaciones más frecuentes fueron ganglionar (50%), lobar (35%) y cerebelosa (5%). La irrupción hacia el sistema ventricular ocurrió en el 43%. La mediana en la escala ICH-GS al ingreso hospitalario fue de 8 puntos: el 49% presentó 5-7 puntos; el 37%, 8-10 puntos, y el 15%, 11-13 puntos. La tasa de mortalidad a 30 días fue del 30%, y el 31% mostró discapacidad grave. La sobrevida a 30 días fue del 92% en pacientes con 5-7 puntos en la escala ICH-GS, mientras que se redujo al 27% en aquellos con 11-13 puntos.

Conclusiones. En México, la HIC representa casi un tercio de las formas de enfermedad vascular cerebral aguda, y la mayoría de los pacientes que la padecen presentan discapacidad funcional grave o muerte a 30 días. La hipertensión es la principal causa, por lo que el control de este importante factor de riesgo debería reducir la carga sanitaria de la HIC.

Palabras clave. Diagnóstico. Epidemiología. Hemorragia intracerebral. Ictus. Pronóstico.