Contents available at **PubMed**
www.clinicalandtranslationalinvestigation.com

Check for updates

Rev Invest Clin. 2022;74(1):51-60

ORIGINAL ARTICLE

Hospital Arrival and Functional Outcome after Intracerebral Hemorrhage

José L. Ruiz-Sandoval[1,2], Javier Aceves-Montoya[3], Erwin Chiquete[4]*, Germán López-Valencia[2], Alejandro Lara-López[5], Manuel Sánchez-González[1], Amado Jiménez-Ruiz[1], Fernando Barinagarrementería[6], Luis Murillo-Bonilla[7], Antonio Arauz-Góngora[8], Fernando Daniel Flores-Silva[4], Carlos Cantú-Brito Silva[4], and the RENAMEVASC Investigators

[1]Department of Neurology, Hospital Civil de Guadalajara Fray Antonio Alcalde, Guadalajara, Jal.; [2]Department of Neurosciences, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Jal.; [3]Department of Medicine, Universidad Autónoma de Sinaloa, Sin.; [4]Department of Neurology and Psychiatry, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City; [5]Department of Physiology, Centro Universitario de Ciencias de la Salud (CUCS), Universidad de Guadalajara, Guadalajara, Jal.; [6]Department of Neurology, Hospital H+, Querétaro, Qro.; [7]Department of Neurology, Facultad de Medicina, Universidad Autónoma de Guadalajara, Guadalajara, Jal.; [8]Stroke Clinic, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

ABSTRACT

Background: Intracerebral hemorrhage (ICH) is associated with an ominous outcome influenced by the time to hospital presentation. **Objective:** This study aims to identify the factors that influence an early hospital arrival after ICH and the relationship with outcome. **Methods:** In this multicenter registry, patients with confirmed ICH on CT scan and well-known time of symptoms onset were studied. Clinical data, arrival conditions, and prognostic scores were analyzed. Multivariate models were built to find independent predictors of < 6 h arrival (logistic regression) and in-hospital death (Cox proportional-hazards model). **Results:** Among the 473 patients analyzed (51% women, median age 63 years), the median delay since onset to admission was 6.25 h (interquartile range: 2.5-24 h); 7.8% arrived in < 1 h, 26.3% in < 3 h, 45.3% in < 6 h, and 62.3% in < 12 h. The in-hospital, 30-day and 90-day case fatality rates were 28.8%, 30.0%, and 32.6%, respectively. Predictors of arrival in < 6 h were hypertension treatment (odds ratios [OR]: 1.675, 95% confidence intervals [CI]: 1.030-2.724), ≥ 3 years of schooling (OR: 1.804, 95% CI: 1.055-3.084), and seizures at ICH onset (OR: 2.416, 95% CI: 1.068-5.465). Predictors of death (56.9% neurological) were systolic blood pressure > 180 mmHg (hazards ratios [HR]: 1.839, 95% CI: 1.031-3.281), ICH score ≥ 3 (HR: 2.302, 95% CI: 1.300-4.074), and admission Glasgow Coma Scale < 8 (HR: 4.497, 95% CI: 2.466-8.199). Early arrival was not associated with outcome at discharge, 30 or 90 days. **Conclusions:** In this study, less than half of patients with ICH arrived to the hospital in < 6 h. However, early arrival was not associated with the short-term outcome in this data set. (REV INVEST CLIN. 2022;74(1):51-60)

Keywords: Arrival. Cerebrovascular. Death. Intracerebral hemorrhage. Outcome. Stroke.

***Corresponding author:**
Erwin Chiquete
E-mail: erwin.chiquetea@incmnsz.mx

Received for publication: 06-09-2021
Approved for publication: 05-11-2021
DOI: 10.24875/RIC.21000471

INTRODUCTION

Intracerebral hemorrhage (ICH) is less studied than other subtypes of cerebrovascular disease, despite higher mortality and worst short- and long-term prognosis compared with other stroke types[1]. In Mexico, ICH accounts for about 30% of all types of stroke, with an acute phase case fatality rate (CFR) ranging from 30% to 50%[2-5]. Despite these alarming data, information regarding pre-hospital characteristics and determinants of ICH is scarce, which contrasts with the knowledge on acute ischemic stroke, a condition where the pre-hospital determinants that favor or delay hospital arrival are well established[6-8]. There is evidence that an early arrival may be beneficial for most of the acute neurovascular syndromes[4-8], and it appears that implementing a stroke code has contributed to prompt hospital admission for all stroke types. This collateral beneficial effect has favored early diagnostic evaluations and prompt therapeutic interventions, such as acute blood pressure control and surgical evacuation, when needed[9,10].

Our aim was to identify the variables determining hospital arrival in the first 6 h after ICH symptoms onset and to analyze their impact on short-term outcome. Our hypothesis was that an early arrival is associated with better prognoses.

METHODS

We analyzed the database from the multicenter RENAMEVASC registry that included all consecutive adult patients with any type of acute stroke confirmed by neuroimaging studies[5]. Briefly, this registry was a hospital-based observational study designed and conducted by the Mexican Association of Cerebral Vascular Disease (AMEVASC) to improve stroke knowledge and awareness in the community, where investigators from 25 referral hospitals of 14 Mexican federal states recruited consecutive patients with an acute stroke diagnosis. All the participants or their legal proxies signed informed consent. An Local Institutional Review Boards approved the study at each participating center.

Definitions of the analyzed sociodemographic variables, risk factors, and clinical conditions at admission were implemented according to international standards at the moment of the study. Hypertension was recorded in patients with primary or secondary hypertension history with either regular or irregular treatment, or determination of arterial blood pressure values ≥ 140/90 mmHg for more than 2 weeks after hospitalization. Alcoholism was defined as a patient with a history of chronic alcohol consumption. Smoking history was determined in patients with current or past tobacco use confirmed by patient or family member at admission. Obesity was registered in patients with body mass index ≥ 30 at hospital admission.

The ICH clinical features at onset were queried in the emergency room, which included headache, vomit, impaired consciousness, motor or sensorial deficits, seizures, and other features. Neurological status was evaluated using the Glasgow coma scale (GCS), and severity of the neurological status was classified as mild (13-15 points), moderate (9-12), or severe (< 8 points). Furthermore, ICH location (i.e., lobar, deep ganglionic, cerebellar, brainstem or intraventricular), etiology (i.e., hypertensive, arteriovenous malformation, amyloid, coagulation disorders, drug use, undetermined), as well as any ventricular system apertures, were recorded. Trauma, ruptured aneurysm, and cerebral venous thrombosis leading to ICH were excluded from the present analysis. The patients with unknown symptom onset, inaccurate registry data at hospital admission, or ICH development while hospitalized for reasons other than the initial stroke, were also excluded from the study.

Hematoma volume was calculated according to the AxBxC/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[11,12]. Established treatment in the acute phase was classified as conservative (i.e., medical) and surgical (i.e., hematoma drainage, ventriculostomy, or both). Two prognostic models were analyzed to estimate 30-day mortality; the ICH score[13] and the ICH-grading scale (GS)[14]. Arrival times were analyzed during the 1st h, 3, and 6 h after ICH symptoms onset. The functional outcome was evaluated using the modified Rankin scale (mRS) at 30 and 90 days. The CFR was also assessed at discharge, 30 and 90 days after ICH onset.

Statistical analysis

Demographic data are presented as simple relative frequencies expressed as percentages. Median with interquartile range (IQR) is used to describe quantitative variables with non-parametric distribution. Normally, distributed quantitative variables are expressed as mean with standard deviation. Pearson's Chi-squared test (or Fisher's exact test, where applicable) was used to compare the frequencies of qualitative nominal variables, between two groups, or to assess the homogeneity in the distribution of variables into three or more groups. Student's t-test was used when comparing two continuous quantitative variables with normal distribution. All p-values were calculated two-sided and considered significant when $p < 0.05$. A multivariate model was built by using binary logistic regression models to find independent variables associated with hospital arrival in < 6 h. Reliability of the model was tested with the Hosmer-Lemeshow goodness-of-fit test, and considered reliable when $p > 0.2$. Multiple iterations were performed up to obtaining the model with the best reliability and plausibility according to variables' characteristics. Results of the binary regression model are presented with the respective odds ratios (OR) and 95% confidence intervals (95% CI). A Cox proportional-hazards model was used to find independent predictors of in-hospital death. Results of the Cox proportional-hazards model are presented with hazards ratios (HRs) with the respective 95% CIs. The IBM-SPSS v25 statistical package was used in all calculations.

RESULTS

From 500 patients with ICH included in this multicenter registry, 473 (94.6%) patients met the selection criteria for the present analysis (51% women, with a median age of 63 years, range: 18-98 years); 63 (13%) were patients under 40 years of age and 176 (37%) over 70 years. The reason for excluding the remaining 27 (5.4%) patients was the lack of data on symptoms onset. The main identified risk factors for ICH were hypertension, obesity, smoking, and alcoholism (Table 1). In all, 244 (51.6%) patients had an indirect arrival (i.e., were referred from other institutions) and received first medical assessment in a first-aid post or first-level medical care before definite reference to the final second- or third-level institution. The median delay from symptoms onset to the first medical evaluation was 1.0 h (IQR: 0.5-3 h). On the other hand, the median time from symptoms onset to final emergency-room admission was 6.25 h (IQR: 2.5-24 h): 37 (7.8%) arrived in < 1 h, 124 (26.3%) in < 3 h, 214 (45.3%) in < 6 h, and 294 (62.3%) in < 12 h. As a consequence, the final arrival time was shorter in patients who were not referred from another institution (i.e., direct arrival), as compared with those patients who received first assessment in a different hospital before final referral (i.e., indirect arrival) (median time: 3.0 vs. 12.0 h, respectively; $p < 0.001$).

At hospital admission 39% of patients had systolic blood pressure (SBP) > 180 mmHg and 33% had glucose levels > 150 mg/dL. The median GCS was 12 (IQR: 8-14), without sex or age differences. In all, 469 (99%) had head CT scan and 4 (1%) underwent MRI. Neuroimaging was obtained at a median of 9.45 h (IQR: 4.5-24 h) since symptoms onset, or 4.0 h (IQR: 3-6 h) on hospital admission (33% underwent neuroimaging in < 6 h since emergency room presentation). However, the time from symptoms onset to undergoing neuroimaging was shorter in patients who had a direct arrival, as compared with those with indirect arrival (median time: 7.3 vs. 11.0 h, respectively; $p = 0.034$). After etiological investigations during the hospital stay, the main cause of ICH was considered arterial hypertension in 70% of patients (64% with a history of hypertension and 6% with diagnosis after ICH), undetermined 9%, cerebral vascular malformations 7%, and amyloid angiopathy in 4% of cases. In all, 9% were receiving antiplatelet therapy, and 2% received anticoagulant before admission. Main ICH locations were supratentorial (91%) and deep (52%). Hematoma volume had a median of 20 mL (IQR: 9-45 mL), with 35% with a volume > 30 mL. Intraventricular hemorrhage occurred in 45% of the cases. A total of 85 (18%) patients received surgical evacuation of hematoma with or without ventriculostomy. The median in-hospital stay length was 9.0 days (IQR: 5-17 days). A total of 112 (23.7%) patients required admission to the intensive care unit, with a median UCI stay length of 5.0 days (IQR: 2.75-9.0 days). In all, 179 (38%) had in-hospital complications such as pneumonia (28%), urinary tract infections (12%), deep-vein thrombosis (6.2%), and other complications.

Table 1. Characteristics at admission of patients with intracerebral hemorrhage

Variables	Total (n= 473)	Men (n = 230)	Women (n = 243)	p-value	Age < 60 y (n = 198)	Age ≥ 60 y (n = 275)	p-value
Educational level, %							
Illiterate	31	24	39	0.001	16	42	0.001
1-6 years	53	57	49	0.032	56	50	–
> 6 years	16	19	14	–	29	7	0.001
Risk factors, %							
Hypertension	64	64	65	–	57	70	0.002
Obesity	33	30	35	–	32	33	–
Smoking	25	37	14	0.001	28	23	0.001
Alcoholism	20	36	5	0.001	23	18	–
Diabetes	16	15	18	–	12	20	–
Ischemic heart disease	6	5	6	–	3	8	0.043
Characteristics at admission, %							
SBP ≥ 180 mmHg	39	36	49	–	36	40	–
Glycemia ≥ 150 mg/dL	33	32	35	–	29	37	–
GCS 13-15	43	44	43	–	50	39	0.019
GCS 9-12	30	30	30	–	26	32	–
GCS ≤ 8	27	26	28	–	24	30	–
ICH characteristics, %							
Supratentorial	91	92	91	–	88	94	0.048
Deep	52	58	46	0.013	44	58	0.004
Lobar	36	30	41	0.021	38	34	–
Infratentorial	7	7	8	–	9	7	–
Intraventricular	45	45	45	–	43	47	–
Prognostic scores, %							
ICH score 0-2	73	73	74	–	84	66	< 0.001
ICH score 3-6	28	30	26	–	19	34	< 0.001
ICH-GS 5-7	43	39	48	–	65	28	< 0.001
ICH-GS 8-13	57	61	52	–	45	72	< 0.001
Surgical evacuation, %	**18**	**18**	**18**	**–**	**19**	**17**	**–**

GCS: Glasgow Coma Scale; ICH: intracerebral hemorrhage; ICH-GS: intracerebral hemorrhage grading scale; mRS: modified Rankin scale; SBP: systolic blood pressure; SD: standard deviation.

In bivariate analyses, school education, hypertension, seizures at ICH onset (11% of patients), admission blood glucose, admission GCS and the ICH score were factors associated with hospital arrival at different cut-off points (Table 2). Seizures (either focal or generalized) were more common in patients with lobar hemorrhages than in the deep location (45% vs. 26%, p = 0.001) Multivariate models for prediction of hospital arrival were reliable and consistent only for the prediction of arrival in < 6 h (Table 3). Thence, previous hypertension drug therapy, ≥ 3 years of schooling, and seizures at ICH onset were the independent predictors of a hospital arrival in < 6 h.

Table 2. Characteristics at admission and outcomes in relation with time from symptoms onset to hospital arrival of patients with intracerebral hemorrhage

Variables	Arrival < 1 h (n = 37)	Arrival ≥ 1 h (n = 436)	p-value	Arrival < 3 h (n = 124)	Arrival ≥ 3 h (n = 349)	p-value	Arrival < 6 h (n = 215)	Arrival ≥ 6 h (n = 258)	p-value
Male sex, %	46	48	–	34	17	–	49	48	–
Age group, %									
< 40	24	12	–	12	14	–	14	12	–
40-69	54	49	–	56	46	–	50	49	–
≥ 70	22	39	–	31	39	–	36	38	–
Educational level, %									
Illiterate	8	31	0.01	26	31	–	25	34	–
1-6	62	49	–	49	50	–	53	48	–
> 6	22	14	–	18	15	–	16	16	–
Risk factors, %									
Hypertension	54	65	–	38	37	–	69	60	0.04
Obesity	27	33	–	30	34	–	32	34	–
Smoking	24	25	–	26	26	–	27	23	–
Alcoholism	14	21	–	19	20	–	19	21	–
Diabetes mellitus	16	17	–	15	16	–	17	16	–
History of stroke	5	7	–	11	5	–	6	7	–
Clinical features at admission, %									
Impaired consciousness	76	66	–	73	65	–	68	65	–
Headache	46	62	–	57	61	–	57	63	–
Vomiting	27	36	–	33	36	–	32	38	–
Motor deficit	35	24	–	27	24	–	28	23	–
Seizures	22	10	0.04	17	9	0.01	15	7	0.01
SBP ≥ 180 mmHg	48	38	–	45	36	–	43	35	–
Glycemia ≥ 150 mg/dL	30	31	–	32	30	–	32	30	0.03
GCS 13-15	27	44	–	42	44	–	41	44	–
GCS 9-12	30	30	–	28	30	–	29	30	–
GCS ≤ 8	46	26	0.03	30	26	–	30	25	–
ICH characteristics, %									
Supratentorial	89	91	–	91	91	–	90	91	–
Deep	38	53	–	50	56	–	55	49	–
Lobar	46	35	–	30	38	–	32	36	–
Infratentorial	8	7	–	9	7	–	9	6	–
Intraventricular	43	45	–	44	46	–	43	46	–
Volume > 30 mL	38	35	–	35	35	–	38	33	–

(Continues)

Table 2. Characteristics at admission and outcomes in relation with time from symptoms onset to hospital arrival of patients with intracerebral hemorrhage *(continued)*

Variables	Arrival < 1 h (n = 37)	Arrival ≥ 1 h (n = 436)	p-value	Arrival < 3 h (n = 124)	Arrival ≥ 3 h (n = 349)	p-value	Arrival < 6 h (n = 215)	Arrival ≥ 6 h (n = 258)	p-value
Prognostic scores, %									
ICH score 0-2	62	74	–	71	7	–	67	78	0.04
ICH score 3-6	43	27	–	32	26	–	35	22	0.02
ICH-GS 5-7	38	44	–	43	43	–	40	46	–
ICH-GS 8-13	62	56	–	57	57	–	60	54	–
Surgical treatment, %	8	19	–	15	19	–	16	19	–
Outcomes, %									
mRS 0-2 at 30 days	16	20	–	20	19	–	19	20	
mRS 0-2 at 3 months	39	52	–	35	55	0.04	41	57	–
Death at 30 days	46	29	0.03	34	28	–	34	27	–
Death at 3 months	8	7	–	14	5	–	12	9	–

GCS: Glasgow Coma Scale; ICH: intracerebral hemorrhage; ICH-GS: intracerebral hemorrhage grading scale; mRS: modified Rankin scale; SBP: systolic blood pressure; SD: standard deviation.

CFR at discharge, 30 days and 90 days after ICH onset was 28.8%, 30.0%, and 32.6%, respectively. The causes of death were neurological in 56.9%, systemic (non-neurological, such as sepsis) in 27.5%, and pertaining to both categories of causes in 15.7%. Correspondingly, mRS > 3 at discharge, 30 days and 90 days was 71.7%, 61.4%, and 56.2%, respectively (21.6% 90-day improvement). The median mRS at discharge, 30-day and 90-day follow-up was essentially unchanged, with 4 (IQR: 3-6), 4 (IQR: 3-6), and 4 (IQR: 2-6), respectively. In a Cox proportional-hazards model for prediction of in-hospital death, SBP > 180 mmHg at admission, ICH score ≥3, and GCS <8 at admission were the independent predictors (Table 4). Notably, arrival time, indirect arrival (after referral from another institution), ICH-GS, clinical features at onset or comorbidities were not independent predictors, but they were retained in the final multivariate model for adjustment.

DISCUSSION

Conditions that delay or facilitate hospital arrival have been frequently studied in ischemic stroke, even before the approval of intravenous thrombolysis with tissue plasminogen activator[15,16]. The diversity of diagnostic studies and time-dependent treatment options in cerebral infarction has kept the interest in this topic constant[17-20]. In contrast, specific determinants for early or late hospital arrival for ICH have been scarcely studied[7,21-23]. In our study, more than 50% of patients with spontaneous ICH had a medical assessment in a first-aid post or first-level institution that finally referred the patient to a different medical care center that took the responsibility to admit and treat the patient, losing a median time of 5.25 h, which might be essential to improve the outcome in some cases. Moreover, a quarter of patients had an early hospital arrival within the first 3 h, and nearly 50% had an early arrival in the first 6 h. In a similar contemporary study from Brazil, 64% of patients had a hospital arrival within the first 3 h[24]. In the Spanish multicenter stroke registry, EPICES, which analyzed the hospital arrival times and delay before acute stroke patients received neurological care, 35% of patients (among 5,454 of all stroke types) arrived in < 1 h, 64% < 3 h, and 78% in < 6 h from the onset of acute cerebrovascular disease[25]. In the same report, 771 patients with ICH had an average time to

Table 3. Binary logistic regression model for the prediction of a hospital arrival in < 6 h*

Variables	Odds ratio	95% CI	p-value
Hypertension treatment	1.675	1.030-2.724	0.038
≥3 years of schooling	1.804	1.055-3.084	0.031
Seizures at ICH onset	2.416	1.068-5.465	0.034

*Model adjusted by age, sex, family history of stroke, personal history of stroke, obesity, hypertension, diabetes, smoking, alcoholism, a nd clinical features at ICH onset. Hosmer-Lemeshow test for goodness-of-fit in final step of the regression model: chi-square = 2.81, 3 df, p = 0.591. Only independent variables significantly associated are shown. ICH: intracerebral hemorrhage.

Table 4. Cox proportional hazards model for the prediction of in-hospital death*

Variables	Hazard ratio	95% CI	p-value
SBP > 180 mmHg at admission	1.839	1.031-3.281	0.039
ICH score ≥ 3	2.302	1.300-4.074	0.004
GCS < 8 at admission	4.497	2.466-8.199	< 0.001

*Model adjusted by age, sex, family history of stroke, personal history of stroke, obesity, hypertension, diabetes, smoking, alcoholism, a nd clinical features at ICH onset. Hosmer-Lemeshow test for goodness-of-fit in final step of the regression model: chi-square = 2.81, 3 df, p = 0.591. Only independent variables significantly associated are shown. SBP: systolic blood pressure; ICH: intracerebral hemorrhage; GCS: Glasgow Coma Scale.

hospital arrival of 3.8 h, being the hypertensive etiology with the shortest arrival time with an average of 3.17 h, compared to other ICH causes. In a recent report from Korea analyzing the type of emergency medical service use on the time interval from ICH onset to hospital admission they found that, among 6,564 patients, there was an emergency arrival within the first hour in 23.7% of patients, particularly in those that used the emergency system with direct referral[23]. Extensive data analysis between 1990 and 2008 from 75 studies and 183,009 stroke patients has reported a 6% decrease in time to hospital arrival per year, with variations depending on the period and study design, geographical or cultural barriers, and pre-hospital organization for stroke care[26].

The precise knowledge of hospital arrival times is relevant for the application of directed interventions in the current management of ICH. Hemostatic therapy, temperature, blood pressure, and glucose control require evaluation in an emergency setting within the first hours after symptoms onset according to current recommendations[9,27-30]. A recent article by Colton et al., emphasizes that early symptom recognition and activation of a stroke code favors an earlier hospital arrival of patients with ICH and shortens other strategies such as door-to-CT scan time frame and other essential interventions[10]. In our report, the median time elapsed from the onset of ICH symptoms to the performance of neuroimaging was 9.45 h (4 h after hospital presentation).

In the present study, we found that prehospital characteristics such as medical treatment, clinical features, and patient's education level are associated with an early arrival. Similarly, arrival characteristics such as prognostic scores and blood pressure were found associated with the short-term outcome. These findings suggest that very early characteristics of ICH patients can predict a prompt hospital presentation and short-term outcome, since it is possible that patients with a severe clinical presentation arrive earlier than those with little neurological impairment. The clinical severity of ICH had been previously found associated with an early hospital arrival after ICH[5,24,31].

We found an independent association between the presence of seizures and early hospital arrival. Seizures were more common in patients with lobar hemorrhages than in deep location, which is in accordance with the literature[32]. It is possible that witnessing a seizure in our environment translates into a cardinal event for seeking medical care. Perceptions, myths and orally transmitted knowledge about epilepsy could be also considered as potential influence[33].

In the bivariate analyses, we found that GCS and ICH score were associated with early arrival at some time points. This finding can be associated with a worse clinical state being more likely to receive a prompt medical attention, reference, and diagnostic evaluation. However, to our surprise the time to hospital arrival was not independently associated with outcome in the multivariate analysis, which could have been analytically overcome by the clinical state itself, reflected by the prognostic scores.

Although ICH usually implies a poor prognosis, determining factors of the outcome are characteristics and severity of the hematoma, such as volume, location and intraventricular irruption[9,14]. However, small hemorrhages can present with minor symptoms as a lacunar stroke syndrome, which are associated with a good outcome and CFR fewer than 10%[34,35]. Moreover, the site of bleeding is the second most important hematoma variable that determines the outcome, especially for infratentorial and deep lobar structures[36], since, for example, even small hematomas located in the thalamus are associated with a prognosis comparable to a brainstem ICH[37]. Therefore, it is possible that the more severe hemorrhages are naturally selected for hospitalization and that the worse-case scenarios are over represented in hospital series. In our study, early hospital arrival was not statistically associated with the functional outcome or death in the short term. Our results coincide with those of Naganuma et al., who analyzed 1226 patients with acute ICH and demonstrated that the time elapsed to hospital arrival had no effect on functional prognosis or death in the short term[38]. However, the fact that early arrival might not impact ICH short-term prognosis should not be misinterpreted as evidence justifying delays in the rapid recognition of an acute neurovascular syndrome and transfer to the hospital, especially since at the very beginning it is difficult to distinguish ischemic from hemorrhagic stroke based only on clinical features[4]. Moreover, we do not know the impact of early hospital arrival on the mid- and long-term or for specific outcomes, such as motor, cognitive or non-neurological complications.

In the present cohort only about one-quarter of the patients with ICH were admitted to the ICU, in spite that this condition is considered critical. The limited resources and scarce spaces in ICU may explain this phenomenon, but it may also be explained by cognitive errors such as fatalism and self-fulfilling prophecy influencing medical decisions, and thus, limiting the opportunities to survive to these patients.

Limitations of this study include that we did not consider certain characteristics associated with hospital arrival, such as previous knowledge about stroke symptoms, educational level of bystanders, reasons for arriving indirectly after a hospital referral, and medications used before final hospital admission. Registering of the bystander's education level would also offer more insight into the determinants for a prompt hospital arrival. Furthermore, even when the time to hospital arrival is more likely to be associated with short- instead of long-term outcome, we did not analyze possible impairments and mortality in the long run. Such analysis would provide with more data on the consequences of expedited medical care.

In conclusion, in this multicenter registry from Mexico, nearly half of the patients had an arrival within 6 h. Seizures at ICH onset, patient's basic level of education, and hypertension therapy were the main clinical predictors of early arrival. More severe clinical conditions were associated with short-term mortality. Further studies are necessary to elucidate whether time elapsed from symptoms onset to hospital arrival is determinant for short- and long-term outcome when effective and specific treatments are finally available.

ACKNOWLEDGMENTS

The authors thank AMEVASC for the collective academic support provided. The following centers and investigators from Mexico participated in the RENAMEVASC study: C. Cantú-Brito (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City); A. Arauz-Góngora, L. Murillo-Bonilla and L. Hoyos (Instituto Nacional de Neurología y Neurocirugía, Mexico City); J.L. Ruiz-Sandoval and E. Chiquete (Hospital Civil de Guadalajara, Jalisco); J. Villarreal-Careaga and F. Guzmán-Reyes (Hospital

General de Culiacán, Sinaloa); F. Barinagarrementería (Hospital Angeles de Querétaro, Querétaro); J.A. Fernández (Hospital Juárez, Mexico City); B. Torres (Hospital General de León, Guanajuato); C. León-Jiménez (Hospital General ISSSTE, Zapopan, Jal.); I. Rodríguez-Leyva (Hospital General de San Luis Potosí, San Luis Potosí): R. Rangel-Guerra (Hospital Universitario de Nuevo León, Monterrey, N.L.); M. Baños (Hospital General de Balbuena, Mexico City); L. Espinosa and M. de la Maza, Hospital San José de Monterrey, Nuevo León); H. Colorado (Hospital General ISSSTE, Veracruz, Ver.); M.C. Loy-Gerala (Hospital General de Puebla, Puebla); J. Huebe-Rafool (Hospital General de Pachuca, Hidalgo); G. Aguayo Leytte (Hospital General de Aguascalientes, Aguascalientes); G. Tavera-Guittings (Hospital General ISSSTE, Campeche, Camp.); V. García-Talavera (Hospital IMSS "La Raza", Mexico City); O. Ibarra y M. Segura (Hospital General de Morelia, Morelia); J.L. Sosa (Hospital General de Villahermosa, Tabasco); O. Talamás-Murra (Hospital General ISSSTE, Torreón, Coahuila); M. Alanís-Quiroga (Hospital Universitario de Torreón, Coah.); J.M. Escamilla (Hospital de la Marina Nacional, Mexico City); M.A. Alegría (Hospital Central Militar, Mexico City); J.C. Angulo (Hospital General, Veracruz, Ver.).

REFERENCES

1. Li G, Sun J, Ma K, Yan Q, Zheng X, Qin M, et al. Construction of a cerebral hemorrhage test system operated in real-time. Sci Rep. 2017;7:42842.
2. Cantú-Brito C, Majersik JJ, Sánchez BN, Ruano A, Quiñones G, Arzola J, et al. Hospitalized stroke surveillance in the community of Durango, Mexico: the Brain attack surveillance in Durango study. Stroke. 2010;41:878-84.
3. Arauz A, Márquez-Romero JM, Barboza MA, Serrano F, Artigas C, Murillo-Bonilla LM, et al. Mexican-national institute of neurology and neurosurgery-stroke registry: results of a 25-year hospital-based study. Front Neurol. 2018;9:207.
4. Chiquete E, Sandoval-Rodríguez V, García-Grimshaw M, Jiménez-Ruiz A, Gómez-Piña JJ, Ruiz-Ruiz E, et al. Reliability of bystander recognition of clinical features in pre-hospital classification of acute cerebrovascular syndromes: preliminary findings. Rev Invest Clin. 2020;73:20000238.
5. 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.
6. León-Jiménez C, Ruiz-Sandoval JL, Chiquete E, Vega-Arroyo M, Arauz A, Murillo-Bonilla LM, et al. Hospital arrival time and functional outcome after acute ischaemic stroke: results from the PREMIER study. Neurologia. 2014;29:200-9.
7. Chiquete E, Jiménez-Ruiz A, García-Grimshaw M, Domínguez-Moreno R, Rodríguez-Perea E, Trejo-Romero P, et al. Prediction of acute neurovascular syndromes with prehospital clinical features witnessed by bystanders. Neurol Sci. 2021;42:3217-24.
8. Lee KJ, Kim JY, Kang J, Kim BJ, Kim SE, Oh H, et al. Hospital volume and mortality in acute ischemic stroke patients: effect of adjustment for stroke severity. J Stroke Cerebrovasc Dis. 2020;29:104753.
9. Hemphill JC 3rd, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American heart association/American stroke association. Stroke. 2015;46:2032-60.
10. Colton K, Richards CT, Pruitt PB, Mendelson SJ, Holl JL, Naidech AM, et al. Early stroke recognition and time-based emergency care performance metrics for intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29:104552.
11. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. Stroke. 1996;27:1304-5.
12. Sembolini A, Romoli M, Pannacci U, Gambaracci G, Floridi P, Acciarresi M, et al. Acute hematoma expansion after spontaneous intracerebral hemorrhage: risk factors and impact on long-term prognosis. Neurol Sci. 2020;41:2503-9.
13. Hemphill JC 3rd, Bonovich DC, Besmertis L, Manley GT, Johnston SC. The ICH score: a simple, reliable grading scale for intracerebral hemorrhage. Stroke. 2001;32:891-7.
14. Ruiz-Sandoval JL, Chiquete E, Romero-Vargas S, Padilla-Martínez JJ, González-Cornejo S. Grading scale for prediction of outcome in primary intracerebral hemorrhages. Stroke. 2007;38:1641-4.
15. Barsan W, Brott T, Broderick J, Haley E, Levy D, Marler J. Time of hospital presentation in patients with acute stroke. Arch Intern Med 1993;153:2558-61.
16. UK-TIA Study Group. The UK-TIA aspirin trial: interim results. Br Med J. 1988;296:316-20.
17. Johnson-Black P, Wong G, Starkman S, Sanossian N, Sharma L, Kim-Tenser M, et al. A prehospital acute stroke trial has only modest impact on enrollment in concurrent, post-arrival-recruiting stroke trials. J Stroke Cerebrovasc Dis. 2020;29:105200.
18. Reznik ME, Fakhri N, Moody S, Murray K, Costa S, Yaghi S, et al. Arrival blood pressure in hypertensive and non-hypertensive spontaneous intracerebral hemorrhage. J Neurol Sci. 2020; 416:117000.
19. Han TS, Gulli G, Affley B, Fluck D, Fry CH, Barrett C, et al. New evidence-based A1, A2, A3 alarm time zones for transferring thrombolysed patients to hyper-acute stroke units: faster is better. Neurol Sci. 2019;40:1659-65.
20. Griñán K, Arboix A, Massons J, Díez L, Vergés E, Gil F, et al. Cardioembolic stroke: risk factors, clinical features, and early outcome in 956 consecutive patients. Rev Invest Clin. 2020; 73:23-30.
21. Kim S, Shin SD, Ro YS, Song KJ, Lee YJ, Lee EJ, et al. Effect of emergency medical services use on hospital outcomes of acute hemorrhagic stroke. Prehosp Emerg Care. 2016;20:324-32.
22. Cooper D, Jauch E, Flaherty ML. Critical pathways for the management of stroke and intracerebral hemorrhage: a survey of US hospitals. Crit Pathw Cardiol. 2007;6:18-23.
23. Kim DG, Kim YJ, Shin SD, Song KJ, Lee EJ, Lee YJ, et al. Effect of emergency medical service use on time interval from symptom onset to hospital admission for definitive care among patients with intracerebral hemorrhage: a multicenter observational study. Clin Exp Emerg Med. 2017;4:168-77.
24. Valiente RA, de Miranda-Alves MA, Silva GS, Gomes DL, Brucki SM, Rocha MS, et al. Clinical features associated with early hospital arrival after acute intracerebral hemorrhage: challenges for new trials. Cerebrovasc Dis. 2008;26:404-8.
25. Castillo J, Vivancos-Mora J, The EPICES Investigators. Hospital arrival times and delay before acute stroke patients receive neurological care. Analysis of a national multi-centre registry: EPICES registry (II). Rev Neurol. 2012;54:461-7.
26. Evenson KR, Foraker R, Morris DL, Rosamond WD. A comprehensive review of pre-hospital and in-hospital delay times in acute stroke care. Int J Stroke. 2009;4:187-99.
27. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355-65.
28. Qureshi AI, Foster LD, Lobanova I, Huang W, Suarez JI. Intensive blood pressure lowering in patients with moderate to severe grade acute cerebral hemorrhage: post hoc analysis of antihypertensive treatment of acute cerebral hemorrhage (ATACH)-2 trial. Cerebrovasc Dis. 2020;49:244-52.
29. Andalib S, Lattanzi S, Di Napoli M, Petersen A, Biller J, Kulik T, et al. Blood pressure variability: a new predicting factor for clinical outcomes of intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29:105340.

30. Okazaki S, Yamamoto H, Foster LD, Fukuda-Doi M, Koga M, Ihara M, et al. Late neurological deterioration after acute intracerebral hemorrhage: a post hoc analysis of the ATACH-2 trial. Cerebrovasc Dis. 2020;49:26-31.
31. Huttner HB, Kohrmann M, Tognoni E, Juttler E, Richter G, Dorfler A, et al. Clinical severity predicts time to hospital admission in patients with spontaneous intracerebral hemorrhage. Cerebrovasc Dis. 2008;25:533-8.
32. De Herdt V, Dumont F, Hénon H, Derambure P, Vonck K, Leys D, et al. Early seizures in intracerebral hemorrhage: incidence, associated factors, and outcome. Neurology. 2011;77:1794-800.
33. Carod-Artal FJ, Vázquez-Cabrera CB. An anthopological study about epilepsy in native tribes from Central and South America. Epilepsia. 2007;48:886-93.
34. Arboix A, García-Eroles L, Massons J, Oliveres M, Targa C. Hemorrhagic lacunar stroke. Cerebrovasc Dis. 2000;10:229-34.
35. Lioutas VA, Beiser A, Himali J, Aparicio H, Romero JR, DeCarli C, et al. Lacunar infarcts and intracerebral hemorrhage differences: a nested case-control analysis in the FHS (Framingham heart study). Stroke. 2017;48:486-9.
36. Arboix A, Comes E, García-Eroles L, Massons J, Oliveres M, Balcells M, Targa C. Site of bleeding and early outcome in primary intracerebral hemorrhage. Acta Neurol Scand. 2002; 105:282-8.
37. Ruiz-Sandoval JL, Chiquete E, Parra-Romero G, Carrillo-Loza K, Parada-Garza JD, Pérez-Gómez HR, et al. Hypertensive thalamic hemorrhage: analysis of short-term outcome. Int J Neurosci. 2019;129:189-94.
38. Naganuma M, Toyoda K, Nonogi H, Yokota C, Koga M, Yokoyama H, et al. Early hospital arrival improves outcome at discharge in ischemic but not hemorrhagic stroke: a prospective multicenter study. Cerebrovasc Dis. 2009;28:33-8.