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ORIGINAL ARTICLE

Reliability of Bystander Recognition of Clinical Features in Pre-Hospital Classification of Acute Cerebrovascular Syndromes: Preliminary Findings

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ABSTRACT

Background: The recognition of stroke symptoms by patients or bystanders directly affects the outcomes of patients with acute cerebrovascular disease. **Objective:** The objective of the study was to assess the predictive value of the medical history and clinical features recognized by the patients' bystanders to classify neurovascular syndromes in pre-hospital settings. **Methods:** We included 150 stroke patients of two Mexican referral centers: 50 with acute ischemic stroke (AIS), 50 with intracerebral hemorrhage (ICH), and 50 with subarachnoid hemorrhage (SAH). The performance of clinical prediction rules (CPR) to identify the stroke types was evaluated with features recognized by the patients' bystanders before hospital arrival. The impact of CPRs on early arrival and in-hospital mortality was also analyzed. **Results:** Overall, 72% of the patients had previous medical evaluations in other centers before final referral to our hospitals, and therefore, only 45% had a final onset-to-door time <6 h, even when the first medical assessment had occurred in ≤1 h in 75% of cases. Clinical features noticed by the patients' bystanders had low positive predictive values (PPV) for any stroke type. The CPR "language or speech disorder + focal motor deficit" had 93% sensitivity and a negative predictive value (NPV) of 84% to distinguish AIS. In SAH, headache alone showed a sensitivity of 84% and NPV of 97%. No CPR had an adequate performance on ICH. CPRs were not associated with final onset-to-door time. Altered consciousness, age ≥65 years, indirect arrival with stops before final referral, and atrial fibrillation increased in-hospital mortality. **Conclusion:** Clinical features referred by the witness of a neurovascular emergency have limited PPV, but adequate NPV in ruling-out AIS and SAH among stroke types. The use of CPRs had no impact on onset-to-door time or in-hospital mortality when the final arrival to a third-level center occurs with previous medical referrals. (REV INVEST CLIN. 2021;73(2):87-93)

Key words: Acute ischemic stroke. Clinical manifestations. Intracerebral hemorrhage. Prognosis. Subarachnoid hemorrhage.

INTRODUCTION

Initial and timely recognition of an acute stroke by the event's witness is a factor that directly affects the outcome and functional prognosis in all neurovascular emergencies[1-4]. The pre-hospital classification of other vascular emergencies, such as acute coronary syndrome, has proven to shorten the response time by the emergency medical system (EMS), improving the short-term prognosis[5,6]. In ischemic stroke, a short time from symptom onset to clinical assessment makes patients eligible for reperfusion therapies[7-9]. In the setting of a neurovascular emergency, the pre-classification of the stroke type by the EMS may reduce the time to treatment, which may improve clinical outcomes.

The primary objective of the present study was to investigate the predictive value of the patients' past medical history and early clinical features, recognized by a subject witnessing the event, to be used in the pre-hospital classification of the most common stroke types (e.g., ischemic, hemorrhagic, or subarachnoid hemorrhage [SAH]), according to subsequent neuroimaging studies. With this pre-hospital information (i.e., past medical history and clinical features recognized by witnesses), we created clinical prediction rules (CPRs). Thus, a secondary objective was to determine the possible impact of CPRs on the outcome at discharge. With these analyses, we explored the feasibility of a pre-hospital classification of stroke types before ambulance dispatch and its impact on short-term outcome.

METHODS

In this prospective study, we included patients treated at the *Hospital Civil de Guadalajara Fray Antonio Alcalde* (Guadalajara, Jalisco) (n = 99) and at the *Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán* (Mexico City) (n = 51) with a confirmed neuroimaging diagnosis as the gold standard (computed tomography or magnetic resonance imaging) of acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and SAH. The local ethics committees of both hospitals approved the protocol. We randomly selected 50 cases of each of the three included stroke types (AIS, ICH, or SAH) from a larger prospective database on stroke patients, excluding cases of transient ischemic attack or cerebral venous thrombosis. These case records were selected among patients hospitalized in each center from January 2011 to December 2015. Although the proportions of stroke types differ (AIS being the most common), the random selection of stroke syndromes was performed unbiased at an equal quota to balance the statistical analyses on the prediction of stroke types using the bystanders' reference. The stroke onset was defined by the time the patient was last seen to be well, as referred by the subject who witnessing the event. The time of admission was considered as the time of arrival registered in the emergency department (ED). An indirect arrival (with stops or detours) was considered as any arrival to a first-aid service, clinic, or hospital before arriving at our center. Cases in which the onset of clinical manifestations could not be accurately determined, those in which the stroke occurred during sleep or during any hospital stay, and cases with incomplete information on the clinical records were also excluded from the study. We collected the data with a standardized structured case report format (CRF) specifically created for the purposes of the study to be used in a homogeneous and standard fashion by a total of two trained researchers, one per participating center. This CRF has been previously used in other multicenter research projects in Mexico[10] and included the patient's demographic characteristics, past medical history, and pre-hospital clinical manifestations (gathered from the subject who witnessed the event). The clinical features were grouped into the pre-established neurovascular categories. The data were collected by interviewing directly the patient, the patient's family, or any other proxy who witnessed the onset of the neurovascular syndrome.

Clinical evaluations reported by attending physicians were excluded, and only the data provided by the witness was analyzed to emulate a telephone interview between a member of the EMS and the initial witness of the event. We performed this task to assess whether the results of a pre-hospital classification could be easily applied by EMS personnel to identify the stroke subtype before the ambulance dispatch or arrival of the patient to the ED. At present (and at the time the study was carried out), there is no telephone triage in Mexico done by EMS to pre-classify a neurovascular syndrome. Level of consciousness was classified using the bystanders' reference on the patients' behavior as follows: alert, lethargy, somnolence,

Table 1. Baseline characteristics of the 150 patients included in the study

Characteristics	Stroke type			p-value*
	AIS (n=50)	ICH (n=50)	SAH (n=50)	
Age, years, median (range)	68 (25-87)	58 (28-98)	58 (22-77)	0.24
Female, sex, n (%)	32 (64.0)	21 (42.0)	31 (62)	0.05
Educational level, ≥6 years, n (%)	37 (74.0)	43 (86.0)	47 (94.0)	0.02
Risk factors				
Arterial hypertension, n (%)	27 (54.0)	38 (74.0)	26 (52.0)	0.02
Obesity, n (%)	21 (42.0)	23 (46.0)	34 (68.0)	0.02
Diabetes mellitus, n (%)	14 (28.0)	15 (30.0)	10 (20.0)	0.48
Previous stroke, n (%)	12 (24.0)	11 (22.0)	2 (4.0)	0.02
Atrial fibrillation, n (%)	9 (18.0)	3 (6.0)	1 (2.0)	0.01
Clinical features				
Language or speech disorder, n (%)	49 (98.0)	42 (84.0)	29 (58.0)	<0.001
Focal motor deficit, n (%)	47 (94.0)	46 (92.0)	32 (64.0)	<0.001
Headache, n (%)	18 (36.0)	18 (36.0)	41 (82.0)	<0.001
Vomiting, n (%)	9 (18.0)	20 (40.0)	36 (72.0)	<0.001
Altered level of consciousness, n (%)	7 (14.0)	20 (40.0)	32 (64.0)	<0.001

*Comparison between stroke types was performed with χ^2 and Kruskal–Wallis test. AIS: acute ischemic stroke; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage.

stupor, and coma. An altered level of consciousness was considered any state different to alert (i.e., normal awake and response state). Final onset-to-door time was defined as the time from stroke symptoms onset (or the time of "last seen well") to final hospital arrival to our referral centers.

Demographic data, risk factors, and clinical characteristics are presented as measures of central tendency. Analyses of differences between categorical variables were performed with the Fisher χ^2 test, as for the non-parametric continuous variables, the Mann–Whitney U-test, and the Kruskal–Wallis test were used. The Spearman rho correlation was used in the continuous association between two variables. To find prediction variables between arrival time and hospital mortality, we conducted a binary logistic regression, including the independent co-variables with a p ≤ 0.1. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. The model adjustment was evaluated by the Hosmer–Lemeshow goodness of fit test,

which was considered as reliable when p ≥ 0.20. We calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to evaluate different clinical models for distinguishing between stroke types. Since the time for hospital arrival and the in-hospital mortality are multicausal dependent variables, only the results of multivariate analysis are considered in the explanation of cause and effect phenomena, which is why they are the only ones discussed here. All values were two-tailed and considered significant when the p ≤ 0.05. Statistical package SPSS v24.0 (IBM; USA) and EBM v1.2 (Toronto, Ontario; Canada) were used for all calculations.

RESULTS

The study included 150 patients with acute neurovascular syndromes (69 men and 81 women), with a median age of 62 years (range: 21-98 years) (Table 1). There were no significant differences between the two

Table 2. Multivariate analysis of factors associated with in-hospital mortality

Variable	OR 95% CI	p-value*
Age ≥65 years	3.98 (1.38-10.09)	0.01
Indirect arrival with previous stops	5.77 (1.35-22.13)	0.02
Altered level of consciousness	10.58 (3.38-31.39)	<0.001
Atrial fibrillation	12.49 (1.78-77.15)	0.01

*Model adjusted for sex, education level, past medical history, and clinical manifestations (Hosmer–Lemeshow goodness of fit test: χ^2: 5.4, 5 df, p = 0.59).
Only variables significantly associated with the final model are included in the table.
CI: confidence interval.
OR: Odds ratios.

participating centers concerning clinical features, critical times of medical evaluations and arrivals, or outcomes. None of the patients studied were referred to another institution after final arrival to our two participating centers. In all, 72% of the patients had at least one previous medical evaluation in other centers before final referral to our hospitals, and as a consequence, only 28% of the patients had a direct arrival to our centers without a previous referral from another hospital: 14 (28%) with AIS, 15 (30%) with ICH, and 13 (26%) with SAH. Nonetheless, 113 (75.3%) patients had their first medical evaluation in <1 h, which indicates a generally fast reaction by the patients' bystander. The first medical evaluation in <1 h occurred in 40 (80%) AIS patients, in 38 (76%) ICH patients, and in 35 (70%) patients with SAH.

Only 38 (25.3%) patients arrived to the EDs of our centers (final onset-to door time) in < 3 h: 18 (36%) with AIS, 11 (22%) with ICH, and 9 (18%) with SAH (p = 0.09). In turn, 67 (44.7%) patients presented to our hospitals in <6 h: 27 (54%) with AIS, 22 (44%) with ICH, and 18 (36%) with SAH (p = 0.19). The most common clinical manifestation noticed by the patient's bystander was a focal motor deficit (mono or hemiparesis) in 125 (83.3%) patients followed by language or speech disorder (aphasia or dysarthria) in 120 (80%) patients.

Supplemental Tables 1-3 describe the performance of the past medical history, clinical features, and some clinical rules for discrimination between the studied neurovascular syndromes. Overall, we found that relying on clinical features noticed by a witness alone has a low PPV for correctly predicting a stroke. The clinical rule consisting of language or speech disorder + focal motor deficit presented high sensitivity (93.1%) and NPV (84%) to distinguish AIS from ICH and SAH

(Supplemental Table 1). For the detection of ICH, the combination of focal motor deficit + history of hypertension performed better for discrimination among stroke subtypes (sensitivity 71.6%, specificity 56.2%, PPV 61.3%, and NPV 66.6%). However, the separate analysis of those two variables showed better performance at the cost of lower sensitivity and PPV (Supplemental Table 2). We can observe a similar pattern for SAH, in which headache was the most reliable symptom to distinguish among stroke subtypes (sensitivity 84.1% and specificity 63.6%) with a low PPV (22.8%) and high NPV (97.1%). Headache alone was even better than the clinical rule of "headache + vomiting + an altered level of consciousness" (Supplemental Table 3).

The clinical manifestations did not influence the final onset-to-door time within the first hour. A multivariate analysis to evaluate the putative influence of the clinical features on the final onset-to-door time showed that age ≥65 years (OR: 5.59, 95% CI: 1.67–17.57; p = 0.004) and arrival to the hospital without detours or stops along the way (OR: 17.25, 95% CI: 4.60–54.13; p < 0.001) were the only factors associated with a shorter final onset-to-door time (Supplemental Table 4). Overall, in-hospital mortality (i.e., case fatality rate) was 38.7%, higher for SAH (48%) and ICH (40%) than for AIS (28%). The cause of death was deemed neurological in 69%, and no neurological in 31%, mainly sepsis (76%), venous thromboembolism (21%), and other systemic causes (3%). In a multivariate analysis aimed to find factors associated with in-hospital mortality, we found that age ≥65 years, indirect arrival with previous stops, history of atrial fibrillation, and altered level of consciousness before arrival were directly associated with in-hospital death, regardless of the clinical features, CPRs, or stroke types (Table 2).

DISCUSSION

The recognition of an acute stroke may vary among different populations[10-14]. The communication between the EMS personnel and the bystander witnessing an acute cerebrovascular emergency with pre-established methods has improved clinical outcomes in other countries[3,12,15]. The in-hospital outcome of stroke patients might improve by identifying a neurovascular emergency correctly, regardless of its final etiology[4,5,12,16,17]. Our objective was to determine the feasibility and impact of pre-hospital clinical rules to determine the type of stroke, to assess if CPRs could be used by the EMS personnel to implement rapid treatment strategies, especially for reperfusion therapy of AIS.

In our study, the time to a first medical evaluation in <1 h occurred in 75% of patients, but only 25% arrived to our referral centers in <3 h. This salient discrepancy may reflect that recognition of stroke symptoms by witnesses or the patients is usually opportune, regardless the stroke type, and that in the majority of cases, they are acting rapidly seeking for medical evaluation in <1 h, but that this first medical assessment occurs in a medical center that is not prepared to treat stroke patients, ultimately referring the patients to a dedicated center, and thus, wasting critical time to establish appropriate medical care. This unfortunate fact may be due to a reduced sensitivity of the medical staff or an inadequate hospital infrastructure[11,18,19]. In the ICH and SAH cases, we detected a lower final onset-to-door time, probably because the clinical presentation of these stroke types is usually perceived as more severe[11,12]. We also found that a direct arrival (without detours in other medical institutions) and having an age of 65 years or older are factors associated with a shorter final onset-to-door time and that an indirect arrival before definite referral to our centers was associated with a higher probability of in-hospital death. Older age was associated with a 5-fold increased probability of early arrival, possibly due to increased stroke severity in elderly individuals and a known history of vascular risk factors[20,21]. Seeking medical evaluation in the presence of an acute focal neurological deficit is usually fast, even when those manifestations are not necessarily identified as caused by an acute stroke[1,2,12]. Validated pre-hospital clinical rules already exist[16,17,22-24], and our study did not aim to create new ones. The features included in this analysis were those declared by a bystander witnessing the event and not the ones registered by the healthcare personnel. History of atrial fibrillation could have influenced the case fatality rate through a putative a cardioembolic stroke, a mechanism usually associated with larger infarctions, increased hemorrhagic transformation, and higher recurrence[25,26]. Moreover, atrial fibrillation is also associated with higher mortality after acute hemorrhagic stroke types, and not only in AIS[25]. According to the present analysis, the signs and symptoms referred by the person witnessing the event had a low PPV for correctly predicting the type of stroke. CPRs based on manifestations and known risk factors can be useful to increase the clinical suspicion of an acute stroke[7,24]. However, their role in distinguishing between stroke subtypes is questionable, especially in distinguishing between AIS and ICH due to overlapping clinical presentation. Some clinical features and rules could potentially be used to exclude specific neurovascular syndromes due to high sensitivity and NPV (e.g., "language disorder + motor deficit") to identify AIS. In the case of ICH, the correct prediction in excluding other acute neurovascular syndromes was not possible, but the absence of headache by itself could exclude 97% cases with SAH, which may help in leading the diagnostic approach in this subgroup of patients. Our results cannot endorse the use of clinical rules to accurately pre-classify or determine a stroke subtype to initiate out-of-hospital specialized treatment.

This study has limitations that should be considered to interpret our results correctly. The sample size can be small to identify minor differences in prevalence and outcomes and did not include patients without stroke to compare it among stroke mimics, which is essential to generate mechanisms for fast and efficient dispatch of healthcare attention accurately. A prospective multicenter study with a larger sample, involving the EMS networks and hospitals is needed to prove our hypothesis. It is essential to highlight that our study was not aimed to create diagnostic scores for its employment by the paramedic personnel or in the emergency room, for which validated models exist[16,17,22-24] since the features included in this analysis are those declared by the patient's bystander and not those registered after a formal physical examination performed by

healthcare professionals. The fundamental objective of the present study was to investigate the feasibility and impact of a pre-classification of neurovascular syndromes based on witnesses reference to alert the ambulance dispatch personnel to refer the patient directly an in a timely fashion to a prepared hospital that runs organized stroke care. Nevertheless, although the performance of CPRs based on bystanders reference on patients' symptoms seem to be poor in distinguishing among the three main acute neurovascular syndromes, our study provides important data to construct a dedicated pre-hospital stroke dispatching system. First, we confirm that the patient's family or bystanders react usually fast in seeking for medical assessment, but that this assessment occurs in a center that ultimately transfers the patients to a referral hospital. Moreover, we show that pre-classification CPRs have a good performance in discarding stroke syndromes only, but with poor PPV. This finding suggests that recognition of any acute neurological deficit is more relevant than differentiating among stroke syndromes in a pre-hospital setting. A future line of research would be to assess the impact of predicting AIS subtypes by distinguishing lacunar, large-artery, cardioembolic strokes, and other non-lacunar infarctions, given that lacunar syndromes are characteristic and are usually associated with a better short-term outcome[27].

In conclusion, analysis confirms that the witness of an acute stroke usually acts rapidly and that clinical features recognized by the patients' bystanders have low performance in predicting a specific subtype of stroke. However, some clinical features can be used to exclude the main stroke types and to establish a difference among other acute neurovascular syndromes. We confirmed that pre-hospital factors, such as the type of arrival, age, and level of consciousness, have a negative impact on in-hospital mortality.

SUPPLEMENTARY DATA

Supplementary data are available at Revista de Investigación Clínica online (www.clinicalandtranslational-investigation.com). These data are provided by the corresponding author and published online for the benefit of the reader. The contents of supplementary data are the sole responsibility of the authors.

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