Late Hospital Arrival for Thrombolysis after Stroke in Southern Portugal: Who Is at Risk?

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Background: Delayed hospital arrival remains the main reason for the low rates of thrombolysis in eligible acute ischemic stroke (AIS) patients. The role of socioeconomic and clinical factors for the prehospital delay of AIS remains poor and has never been studied in Portugal. *Objectives*: Describe the socioeconomic and clinical factors leading to delayed hospital admission of AIS patients eligible to thrombolysis. *Methods*: A case-control study with a consecutive thrombolyzed AIS patients from 2010 to 2015. Controls were patients who did not receive thrombolysis because of late hospital arrival. Logistic regression with stepwise forward regression analysis was used to identify independent predictors of delayed admission to receive thrombolysis with intravenous tissue-type plasminogen activator (rtPA). *Results*: Of the 1247 patients admitted with AIS, 76 (6%) arrived on-time and received intravenous rtPA. Controls were 65.8% (146/222) of the total number of patients included in the study. Overall, the mean age was 73 years (±11, 61), a minority were below 60 years, and 43.7% were women. Being beneficiary of social insertion income (odds ratio [OR]: .286; .124-.662, $P = .003$), not having any telephone contact (OR: .145; .039-.536, .004) or having exclusive landline (.055; .014-.210, <.001) and posterior circulation stroke (OR: .266; .087-.811, $P = .020$) decreased the likelihood of hospital arrive on-time rtPA. The use of prehospital ambulance services increased (OR: 6.478; 2.751-15.254, $P < .001$) the odds of ER on-time arrival for thrombolysis. *Conclusions*: Poverty, lack of stroke awareness, or difficulties in requesting immediate medical help are the main factors implicated in late-hospital admission for thrombolysis in AIS. Stroke awareness campaigns, promotion of activation of national emergency number and stroke code can increase the rate of thrombolysis.

Key Words: Thrombolysis—hospital arrival—late—stroke

Introduction

The chain of events leading to the final outcome of stroke patients starts immediately after symptoms onset. Thrombolysis with tissue-type plasminogen activator (rtPA) should be initiated as soon as possible within 4.5 hours after stroke onset.[1] In acute ischemic stroke (AIS) patients with indication of mechanical thrombectomy, bridging rtPA is also recommended and may improve the prognosis.[2,1] Hence, for the majority of AIS patients, rtPA remains the most important reperfusion intervention.

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Unfortunately, only a minority of eligible AIS patients receive rtPA. In the vast majority of countries, delayed hospital arrival remains the main reason for the low rates of thrombolysis in eligible AIS patients.[3] Previous studies in Portugal have shown that only 2 out of 5 stroke patients arrive within the first 3 hours after stroke onset[4]; and the main reason for missing thrombolysis in AIS is late-hospital arrival.[5] Specific clinical characteristics, stroke awareness, socioeconomic status, and prehospital delivery system including prenotification practices are among the factors associated with delayed hospital presentation of AIS patients.[3,5-11] Despite its major importance, the knowledge about the contribution of socioeconomic and clinical factors for the prehospital delay of AIS remains poor. Therefore, we decided to investigate for the first time in our region the socioeconomic and clinical factors leading to delayed hospital admission of AIS patients eligible to thrombolysis.

Methods

Study Area and Stroke Care

This study was conducted in the "Litoral Alentejano" region, a well-defined geographical area of 5308.11 km^2 located in southern Portugal (Fig 1a). It is a predominantly rural region, with homogeneous human development index (mean 0.867). The "Unidade Local de Saúde do Litoral Alentejano" is the sole health unit serving the 100,895 inhabitants of the region. Medical care, including prehospital public emergency medical service (EMS) is public and completely free of charge in the country. Prehospital EMS is coordinated at a national level by the National Institute of Emergency Medicine. Upon calling the free national emergency number (112), the citizen is attended by a paramedic under supervision of a doctor who performs a standardized phone interview. If stroke is suspected and no contraindications are recognized, the stroke code is activated.[12] The patient is rapidly transported by the EMS ambulance with prehospital notification to the closest available stroke unit.[13] If no acute reperfusion intervention is not considered, the patient is also transported by the EMS ambulance to the closest available stroke unit, but without activation of the stroke code. The only available stroke unit and emergency department (ED) in the region is in our hospital to where all AIS patients are transported. However, depending on the specific location, AIS patients under stroke code in the northernmost county of the region "Alcácer do Sal" may be diverted to a closest vicinity public hospital to save 30-40 minutes, located in Setúbal (Fig 1b). AIS candidates for thrombectomy are transferred to the Lisbon metropolitan area using "drip and ship" approach (Fig 1b). The transport time from the farthest point of in the region to the ED using EMS services is maximum 60-70 minutes.

Study Design and Data Source

We performed a case-control study with a consecutive series of AIS patients who arrived to the hospital within the window time to receive rtPA (2010-2015). Controls were patients who did not receive thrombolysis because of late hospital arrival (rtPA could not be administered within the first 4.5 hours after stroke onset). To reduce the effect of clinical practice and weekly variation on the thrombolysis rate,[14,15] only patients admitted late to thrombolysis on the same, previous or in the day after each thrombolyzed patient were selected as controls. To avoid selection bias, patients living in Alcácer do Sal, the boundary referral area for AIS under stroke code was excluded (Figure 1a, b). Due to the potential of being in disadvantage regarding prehospital activation/notification and the changes of the contraindications during the

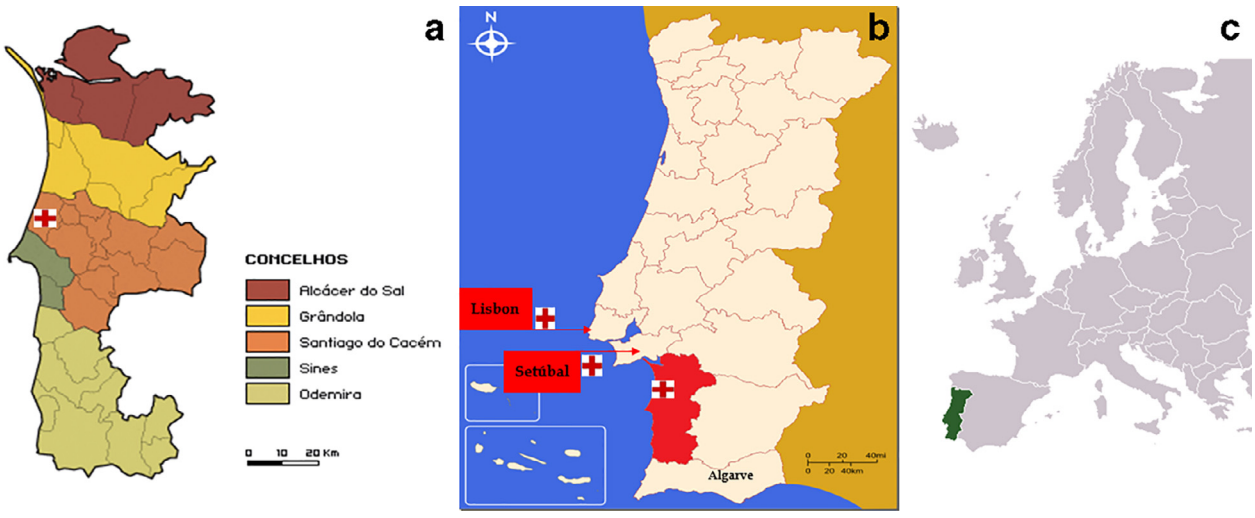

Figure 1. *Map of the "Litoral Alentejano" region, the red cross = emergency room (a); map of "litoral Alentejano" in Portugal showing the proximity to the "Setubal Hospital" and to the capital Lisbon (b); Portugal in Europe (c).*

inclusion period, ineligible for systemic rtPA patients were excluded as controls. The main data source was the hospital and primary health care electronic patient records system that contains demographic data, clinical charts, and paraclinical data including brain imaging. Seven trained medical doctors (SS, IT, TG, JD, DD, JL, and RS) extracted the data. The following variables were available for extraction from the electronic medical charts: age, gender, education level, marital status, availability of telephone contact (exclusive landline, cellular phone, and none), stroke onset place (county), and social insertion income which is an annually given income to help people or families who are in a situation of serious economic need and at risk of social exclusion (these citizens are exempt of copayments), affected arterial territory and severity of stroke using the National Institutes of Health Stroke Scale (NIHSS) score, mode of transportation (prehospital emergency services versus others), time from stroke onset to emergency hospital admission, period of stroke onset along 6-hour time intervals (00:00-5:59; 06:00-11:59; 12:00-17:59; and 18:00-23.59). Prehospital delay or time to presentation was defined as the time from stroke onset to the ED presentation. For patients with wake-up strokes or patients unable to seek help because of altered consciousness, the last time seen without symptoms time was considered as the time of symptom onset.

Statistical Analysis

Differences in baseline variables between patients admitted inside the time window and outside the time window were assessed by chi-square, Student's *t* test or Mann-Whitney U test depending on the variable. Covariables included in the stepwise regression model were selected on the basis of their significance in univariable analysis ($P < .05$). Forward selection with sequential inclusion of sociodemographic variables (1st), mode of transportation and period of stroke onset (2nd), and clinical variables (3rd) was performed with P less than .05 set as inclusion criterion. All analyses used SPSS 21 for Windows (IBM Inc., Armonk, NY). The study was exclusively observational, with no modification of diagnostic procedures and clinical management of patients. All patient data were analyzed after anonymization. The study was approved by the Ethics Committee at our institution.

Results

A total of 1247 patients with AIS were admitted during the study reference period (Fig 2) and 76 (6%) of these, arrived on-time and received rtPA. Controls were 65.8% (n = 146) of the total number (n = 222) of patients included in the study. Baseline characteristics of the patients are shown in Table 1. Overall, the mean age was 73 years (±11, 61), a minority were below 60 years, and 43.7% were women. In comparison to those arriving on time, patients arriving late for thrombolysis ($P < .5$) were more often older than 80 years; beneficiaries of social insertion income; illiterates; singles/widows; and had exclusive landline telephone or did not have any telephone contact (Table 1). Patients admitted within the window time to thrombolysis came to ER more frequently using prehospital emergency services and had more frequently anterior circulation strokes (Table 1). On multivariate analysis (Table 2), being beneficiary of social insertion income

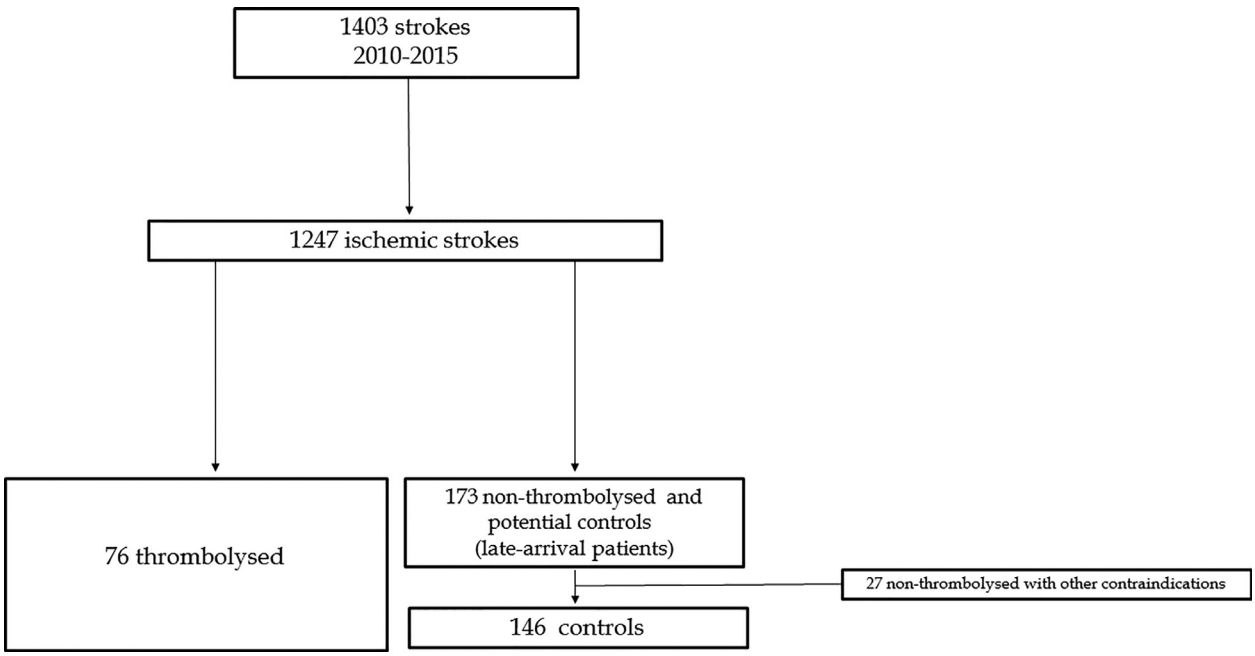

Figure 2. *Data attrition flowchart.*

Table 1. *Baseline characteristics of acute ischemic stroke patients on admission to hospital*

	All patients N = 222 (100%)		On time arrival N = 76 (34.2%)		Late arrival N = 146(65.8%)		*P* value
Gender							
Male	125	(56.3)	43	(56.6)	82	(56.2)	.953
Female	97	(43.7)	33	(43.4)	64	(43.8)	
Age groups							
<60	33	(14.9)	18	(23.7)	15	(10.3)	<.001
60-70	46	(20.7)	22	(28.9)	24	(16.4)	
71-80	85	(38.3)	29	(38.2)	56	(38.4)	
>80	58	(26.1)	7	(9.2)	51	(34.9)	
Stroke onset place (County)							
Outside the area	20	(9.0)	6	(7.9)	14	(9.6)	.062
Grandola	37	(16.7)	14	(18.4)	23	(15.8)	
Odemira	69	(31.1)	19	(25.0)	50	(34.2)	
Sines	36	(16.2)	10	(13.2)	26	(17.8)	
Santiago	60	(27.0)	27	(35.5)	33	(22.6)	
Social insertion income							
Yes	104	(46.8)	23	(30.3)	81	(55.5)	<.001
No	118	(53.2)	53	(69.7)	65	(44.5)	
Education							
Illiterate	30	(13.5)	2	(2.6)	28	(19.2)	<.001
<4 years	64	(28.8)	13	(17.1)	51	(34.9)	
4-12 years	113	(50.9)	55	(72.4)	58	(39.7)	
≥13 years	15	(6.8)	6	(7.9)	9	(6.2)	
Marital status							
Single/widow	83	(37.4)	19	(25.0)	64	(43.8)	.022
Married	107	(48.2)	47	(61.8)	60	(41.1)	
Unknown	12	(5.4)	3	(3.9)	9	(6.2)	
Divorced	20	(9.0)	7	(9.2)	13	(8.9)	
Availability of telephone contact							
Exclusive landline	68	(30.6)	4	(5.3)	64	(43.8)	<.001
None	29	(13.1)	4	(5.3)	25	(17.1)	
Cell phone	125	(56.3)	68	(89.5)	57	(39.0)	
Hospital arrival by prehospital emergency services							
Yes	99	(44.6)	55	(72.4)	44	(30.1)	<.001
No	123	(55.4)	21	(27.6)	102	(69.9)	
Period of the day							
06:00-11:59	115	51.8	30	(39.5)	85	(58.2)	<.001
12:00-17:59	76	34.2	27	(35.5)	49	(33.6)	
18:00-23.59	22	9.9	17	(22.4)	5	(3.4)	
00:00-5:59	9	4.1	2	(2.6)	7	(4.8)	
Admission NIHSS							
≤4	19	8.6	4	(5.3)	15	(10.3)	.227
5-15	125	56.3	48	(63.2)	77	(52.7)	
16-20	44	19.8	11	(14.5)	33	(22.6)	
≥21	34	15.3	13	(17.1)	21	(14.4)	
Vascular territory							
Anterior circulation stroke	174	78.4	68	(89.5)	106	(72.6)	.004
Posterior circulation stroke	48	21.6	8	(10.5)	40	(27.4)	

Abbreviation: NIHSS, National Institutes of Health Stroke Scale.

(odds ratio [OR]: .286; .124-.662), not having any telephone contact (OR: .145;.039-.536) or exclusive landline (OR: .055; .014-.210) and having posterior circulation stroke type (.266; .087-.811) decreased the likelihood of arriving within the window time for rtPA. The use of prehospital ambulance services increased (OR: 6.478; 2.751-15.254) the odds of ER on-time arrival for thrombolysis. A full model of multivariate analysis showing the contribution of all factors ($P < .05$ in univariate analysis) is shown in the supplemental file.

Table 2. *Multivariate logistic regression analysis of factors related to on-time admission within the time window to thrombolysis*

Independent variables	Adjusted OR (CI 95%)	*P*
Social insertion income	.286 (.124-.662)	.003
Availability of telephone contact		
Exclusive landline	.055 (.014-.210)	<.001
None	.145 (.039-.536)	.004
Cell phone	1.000	
Hospital arrival by EMS	6.478 (2.751-15.254)	<.001
Posterior circulation stroke	.266 (.087-.811)	.020

Abbreviation: EMS, emergency medical services.

Discussion

Timely arrival is the biggest hurdle for **r**tPA provision for AIS. Consistently with prior research, the use of emergency ambulance services (EMS) was independently associated with on-time hospital arrival for thrombolysis.[3,6,16,7-11] The small extension of our region probably explains the inexistence of differences between counties located proximal and far from the ED. In addition, EMS services are universal and free in the country, suggesting that awareness and appropriate acute reaction after stroke onset is determining the prehospital delay times. Indeed, a previous study in Portugal showed that lack of stroke awareness contributed to close to a half of hospital delay in an urban region.[5] Social factors such as high education, high income[17,18,10] were predictive of early hospital admission of AIS patients in some studies but not in all.[19,20] Being a beneficiary of social insertion income, not having any phone contact or having exclusive landline telephone decreased the likelihood of arrival in time for thrombolysis. This suggests that poverty, stroke awareness, or difficulties in requesting immediate medical help in the presence of acute neurological deficits, might preclude appropriate emergent assistance. Discrepancy between theoretical stroke knowledge and the reaction in the acute situation appears to be the cause of divergent results of studies addressing the role of sociodemographic factors for the prehospital delay.[21,7] In the northern part of Portugal it was found that stroke awareness was reduced, particularly in the less educated; elderly citizens; and in the rural area as compared to urban areas.[22] Despite the absence of a statistically significant association on regression analysis, it is worthwhile pointing that in rural area such as ours, older patients, and illiterates were more represented in the group of late-admitted. It is uncertain if this is reflecting an underlying pernicious inappropriate seeking behavior or social isolation typical of our rural population, compromising prompt response. We found that having a posterior stroke decreased likelihood of on-time arriving for rtPA treatment. This may reflect unrecognition of posterior stroke signs which was previously demonstrated in the country.[22,23] Under-representation of posterior stroke manifestations in public stroke campaigns probably contributes to this finding.[11] Admission stroke severity has been shown to predict shorter time to hospital admission.[20,6,24,11] Although not statistically significant, patients with severe strokes (NIHSS > 21) were more often admitted on-time to thrombolysis whereas patients with mild strokes (NIHSS < 4) were more often late for thrombolysis. There are important limitations to be considered in our study. The small sample size may have hindered statistically precise results. Generalization is limited because factors and health care organization differs between regions. We did not collect information on other factors that could have influenced the timely arrival for rtPA such as living alone, stroke patients' knowledge or overcrowding in ED. Despite these limitations, our study results are of utmost importance. We were able to show that there is room to improve the rates of thrombolysis by increasing the number of patients arriving on time to the treatment. Stroke awareness campaigns, with emphasis on promotion of activation of national EMS stroke code and lowering the threshold for stroke code to include any acute neurological deficits including posterior stroke manifestations can contribute to progressive increase of thrombolysis rates.

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Supplementary material

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2018.12.009.

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