

Nationwide Access to Endovascular Treatment for Acute Ischemic Stroke in Portugal

Acesso a Tratamento Endovascular para Acidente Vascular Cerebral Isquémico em Portugal



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ABSTRACT

Introduction: Since the publication of endovascular treatment trials and European Stroke Guidelines, Portugal has re-organized stroke healthcare. The nine centers performing endovascular treatment are not equally distributed within the country, which may lead to differential access to endovascular treatment. Our main aim was to perform a descriptive analysis of the main treatment metrics regarding endovascular treatment in mainland Portugal and its administrative districts.

Material and Methods: A retrospective national multicentric cohort study was conducted, including all ischemic stroke patients treated with endovascular treatment in mainland Portugal over two years (July 2015 to June 2017). All endovascular treatment centers contributed to an anonymized database. Demographic, stroke-related and procedure-related variables were collected. Crude endovascular treatment rates were calculated per 100 000 inhabitants for mainland Portugal, and each district and endovascular treatment standardized ratios (indirect age-sex standardization) were also calculated. Patient time metrics were computed as the median time between stroke onset, first-door, and puncture.

Results: A total of 1625 endovascular treatment procedures were registered. The endovascular treatment rate was 8.27/100 000 inhabitants/year. We found regional heterogeneity in endovascular treatment rates (1.58 to 16.53/100 000/year), with higher rates in districts closer to endovascular treatment centers. When analyzed by district, the median time from stroke onset to puncture ranged from 212 to 432 minutes, reflecting regional heterogeneity.

Conclusion: The overall national rate of EVT in the first two years after the organization of EVT-capable centers is one of the highest

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among European countries, however, significant regional disparities were documented. Moreover, stroke-onset-to-first-door times and in-hospital procedural times in the EVT centers were comparable to those reported in the randomized controlled trials performed in high-volume tertiary hospitals.

Keywords: Endovascular Procedures; Ischemic Stroke; Mechanical Thrombolysis; Portugal; Thrombectomy

RESUMO

Introdução: A aprovação do tratamento endovascular para o acidente vascular cerebral isquémico obrigou à reorganização dos cuidados de saúde em Portugal. Os nove centros que realizam tratamento endovascular não estão distribuídos equitativamente pelo território, o que poderá causar acesso diferencial a tratamento. O principal objetivo deste estudo é realizar uma análise descritiva da frequência e métricas temporais do tratamento endovascular em Portugal continental e seus distritos.

Material e Métodos: Estudo de coorte nacional multicêntrico, incluindo todos os doentes com acidente vascular cerebral isquémico submetidos a tratamento endovascular em Portugal continental durante um período de dois anos (julho 2015 a junho 2017). Foram colhidos dados demográficos, relacionados com o acidente vascular cerebral e variáveis do procedimento. Taxas de tratamento endovascular brutas e ajustadas (ajuste indireto a idade e sexo) foram calculadas por 100 000 habitantes/ano para Portugal continental e cada distrito. Métricas de procedimento como tempo entre instalação, primeira porta e punção foram também analisadas.

Resultados: Foram registados 1625 tratamentos endovasculares, indicando uma taxa bruta nacional de tratamento endovascular de 8,27/100 000 habitantes/ano. As taxas de tratamento endovascular entre distritos variaram entre 1,58 e 16,53/100 000/ano, com taxas mais elevadas nos distritos próximos a hospitais com tratamento endovascular. O tempo entre sintomas e punção femoral entre distritos variou entre 212 e 432 minutos.

Conclusão: Portugal continental apresenta uma taxa nacional de tratamento endovascular elevada, apresentando, contudo, assimetrias regionais no acesso. As métricas temporais foram comparáveis com as observadas nos ensaios clínicos piloto.

Palavras-chave: Acidente Vascular Cerebral Isquémico; Portugal; Procedimentos Endovasculares; Trombólise Mecânica; Trombectomia

INTRODUCTION

Endovascular treatment (EVT) is the state-of-the-art treatment for acute ischemic stroke due to large vessel occlusion. It has been estimated that 7% - 13% of acute ischemic stroke patients admitted are eligible for EVT.^{1,2} This number could be as high as 26% when using advanced imaging techniques to select patients.^{2,3}

Since the publication of the EVT trials,⁴⁻⁸ the EVT rate has increased worldwide. However, this growth varies between and within countries. In 2016, Portugal had one of the highest rates of patients with ischemic stroke treated with EVT (4.6%) among European countries, according to the ESO/ESMINT/EAN/SAFE expert survey.⁹ Nevertheless, the distribution of EVT centers in Portugal reflects the population density and existing healthcare resources, namely the network of stroke centers. This distribution may lead to unequal EVT access in more remote areas. However, published data regarding regional disparities within countries is scarce.¹⁰⁻¹³

The network of primary stroke centers and EVT stroke centers in Portugal is organized so that patients initially admitted to a primary stroke center may end up being transferred to an EVT center. Patients who need to be transferred between hospitals for EVT experience longer time from symptom onset to treatment, resulting in worse outcomes in routine clinical practice, even in a country where between-center distances are short.¹⁴ Nevertheless, patients transferred to high-volume centers were found to have reduced mortality compared to patients directly admitted to low-volume centers. Thus, the benefit of treatment in high-volume institutions may outweigh the detrimental effect of hospital transfer.¹⁵

Our main aim was to perform a descriptive analysis of the frequency of EVT in mainland Portugal. We quantified the crude and adjusted rates for all EVTs performed nationally and by administrative districts. As a secondary objective, we described and analyzed differences in time-

-to-treatment metrics.

MATERIAL AND METHODS

Setting

Mainland Portugal has a surface area of 89 015 km², a resident population of 9 792 797 (2017),¹⁶ and a national road network of over 17 000 km. Most of the population lives in areas where road transportation to EVT centers takes under two hours. The stroke code has been gradually implemented in most public hospitals since 2004, while EVT was introduced nationwide during the first semester of 2015. Thus, the study period starts from 2015 to reflect the initial organization of centers capable of performing EVT after the publication of the European guidelines.¹⁷ During the study period, nine stroke centers performed all mainland EVT: four in the North, one in the Center, and four in the Lisbon metropolitan area (Fig. 1). Patients admitted to a primary stroke center would undergo thrombolysis if indicated and then, after contact with the on-call EVT center, would be transferred for further treatment.

Data sources

The analyzed data were obtained from the Portuguese EVT registry (EVT-PT) – a centralized anonymized database specially designed for the present study. The database was built from prospective local registries of consecutive EVT procedures. Data was collected from the registries, collated, and curated from April 2018 to April 2019 (database lock date).

Study design and population

We conducted a retrospective national multicenter cohort study, including all patients treated with EVT for acute ischemic stroke in mainland Portugal between July 1st, 2015, and June 30th, 2017. During the study period, each treating physician determined the indication for EVT procedure and

largely followed the European guidelines published until July 2017.¹⁷ The study was coordinated by the Portuguese Stroke Society (SPAVC), which invited all EVT centers to participate. The study was approved by local Ethics Committees of the different institutions and the Portuguese Data Protection Authority.

Patient characteristics

We analyzed demographic (age, sex, residential postal code), stroke-related (time of stroke onset, time of admission at the first center, time of thrombolytic administration), and procedure-related (time of admission at the second center, if applicable, time of groin puncture) variables. The time of stroke onset was defined as the last time the patient was seen well. Admission times and demographic variables were gathered from administrative records. Treatment times were obtained from medical records and timestamps in digital angiography images. In-hospital stroke patients were defined as patients who were already hospitalized at

symptom onset, regardless of the reason for their hospital admission. The patients' residential postal code was based on their address at the time of stroke. This data was used to map all patients into their corresponding district. The division into districts was based on their limits as defined by article 291 of the Portuguese Constitution, which subdivides mainland Portugal into 18 administrative areas called districts (Fig. 1A).

Statistical analysis

We assessed data integrity and missing information to ensure the quality of the data. Patients residing outside mainland Portugal or patients without a retrievable postal code were excluded from the study, as this data was imperative for rate calculations. In-hospital stroke code activations (which allowed for a chain of care that would not be comparable to activations outside the hospitals), and those patients whose stroke onset, admission, or puncture times were unknown were excluded from time calculations.

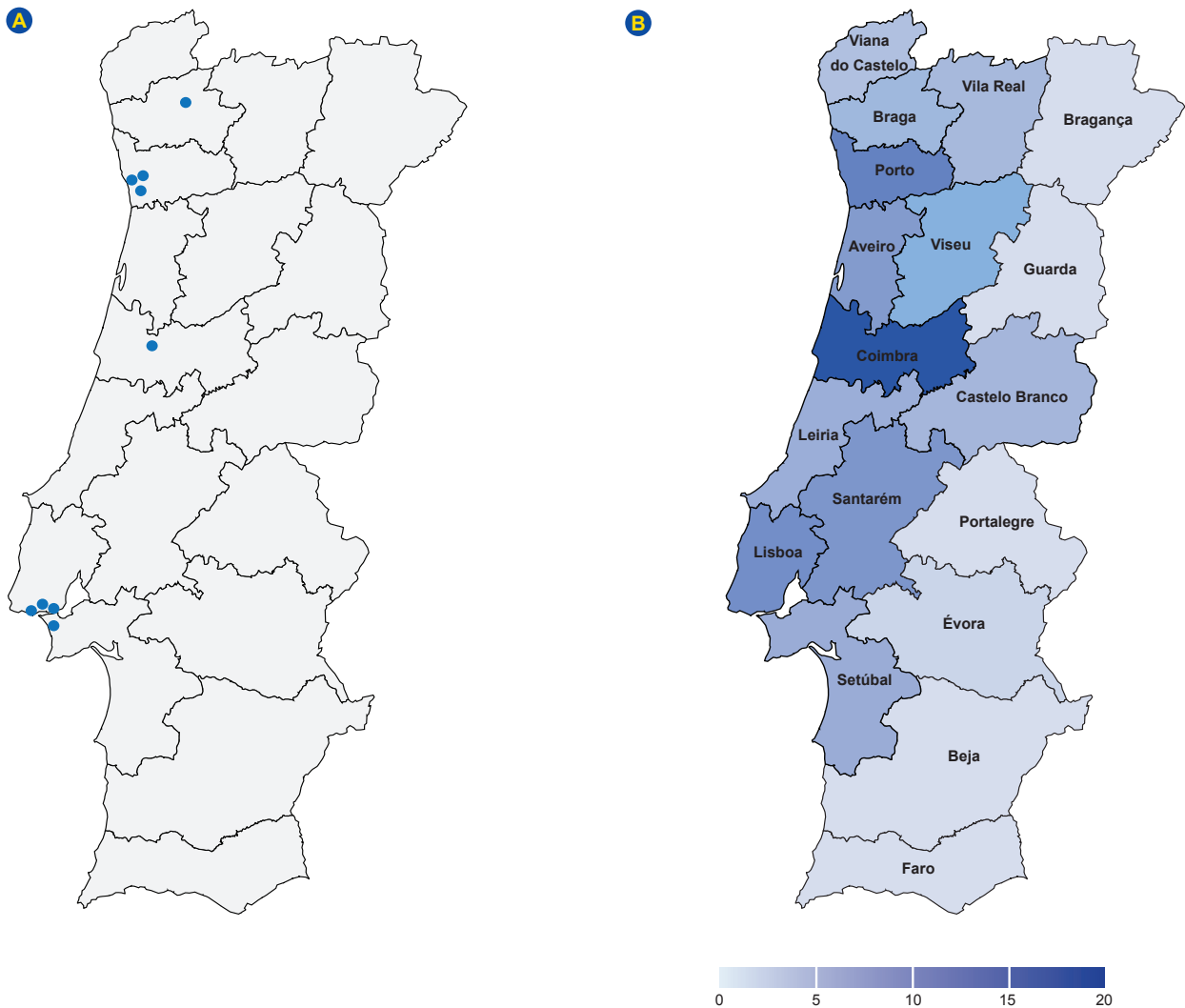


Figure 1 – (A) Portugal map depicting the location of all comprehensive stroke centers (blue dots); (B) EVT rates for the study period per district (scale represents EVT rates per 100 000 inhabitants/year).

Patient characteristics were summarized according to a variable distribution. Crude EVT rates were calculated per 100 000 inhabitants for mainland Portugal and for each district. Rates were calculated for the whole study period, year one (July 2015 – June 2016) and year two (July 2016 – June 2017). Indirect standardization was carried out using the Portuguese 2016 population as reference.¹⁸ The standardized event (EVT) ratio (SER) was computed as the *ratio* between the numbers of events observed and events expected in each district. The number of events expected for each district was calculated based on the national EVT rates standardized using the Portuguese 2016 population as reference.¹⁸ The SER was used to signal districts with rates larger (SER > 1) or lower (SER < 1) than the overall national EVT rates.

Time metrics were defined in minutes and included the time from onset to first-door, from first-door to puncture, and from onset to puncture. The first-door-to-puncture time was defined as the time between the first admission and

the groin puncture, both for patients presented directly to an EVT center and patients that presented first to a primary stroke center. The specific time from arrival at the EVT center to puncture was also calculated both for patients transferred and primary admissions to EVT centers. The data on time to treatment were summarized using their median [interquartile range (IQR)] and computed for the whole period, across years one and two, per district and per transfer status. Statistical comparisons between transferred vs. non-transferred patients, year one *versus* year two, and in-hospital strokes vs. outpatient strokes were calculated using the Wilcoxon rank-sum test. Geographical differences were represented using color-graded maps generated using Highmaps®. All calculations used IBM SPSS Statistics® 25.0.

RESULTS

Geographical distribution of EVT rates

During the study period, 1640 EVTs were performed. Fifteen patients were excluded due to living outside

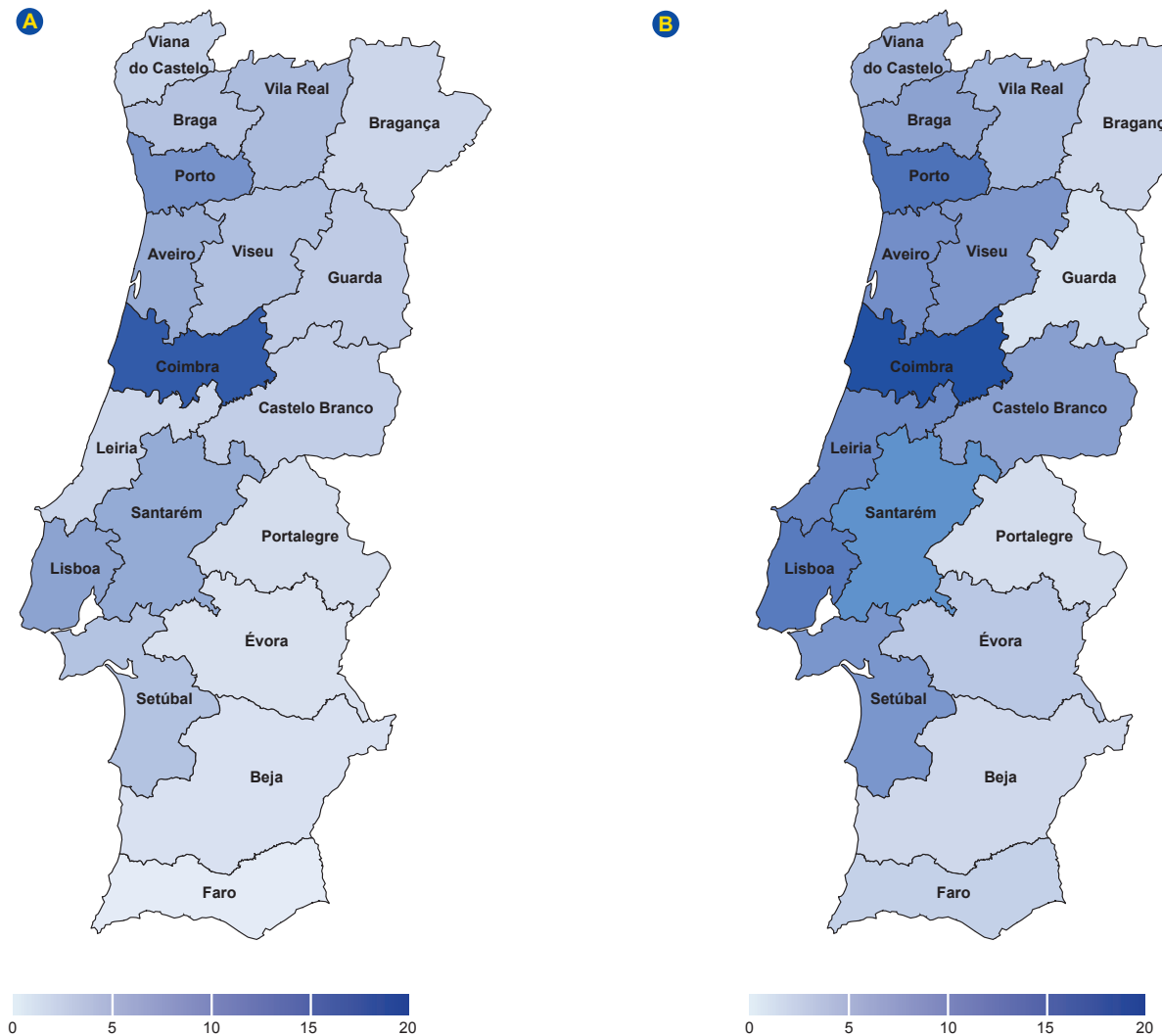


Figure 2 – (A) EVT rates in the first year, per district; (B) EVT rates in the second year, per district (scales represent EVT rates per 100 000 inhabitants for each year).

mainland Portugal (13 from other countries and two from Azores/Madeira), leading to a final inclusion of 1625 EVT patients. The median age of patients was 75 years (IQR 64 - 81) and 54.9% (n = 892) were female. Patients who were 80 years old or older accounted for 32.1% of EVTs (n = 521; 28.2% in year one; 34.5% in year two).

The study period's EVT rate was 8.27/100 000 inhabitants/year, increasing from year one (6.41/100 000 inhabitants) to year two (10.13/100 000 inhabitants per year) in almost all districts (Fig. 2). However, EVT rates were markedly heterogeneous between regions (from 1.58/100 000/year to 16.53/100 000/year), being higher in districts closer to the EVT centers, where EVT is performed (Fig. 1B). This heterogeneity remained after applying the indirect age-standardized method, using the Portuguese 2016 population as the standard, with an SER ranging between 0.14 and 1.44 during the study period [Appendix 1, Fig. 1A (Appendix_01: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_01.pdf)]. The SER also increased from year one to year two in almost all districts [Appendix 1, Figs. 1B, 1C (Appendix_01: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_01.pdf)].

Time metrics

For this analysis, in-hospital stroke code activations (n = 83; 5.1%) were excluded, and a total of 1542 EVT procedures performed during the study period (including patients admitted directly to an EVT center and patients transferred from a primary stroke center) was considered. The me-

dian stroke-onset-to-first-door time was 87 minutes (IQR 60-142), the median first-door-to-puncture time was 156 minutes (IQR 107 - 232), and the median stroke-onset-to-puncture time was 272 minutes (IQR 205 - 355) (Table 1). During the study period, the number of patients transferred between centers increased from year one (49.8%, n = 299) to year two (60.4%, n = 569) (Table 1).

When analyzing the data by district, the median time from stroke onset to first door ranged between 44 and 230 minutes, the median time from first-door to puncture between 114 and 312 minutes, and the median time from stroke onset to puncture between 212 and 432 minutes. Fig. 3 shows the differences between year one and two for door-to-puncture times by district. Regarding the evolution of national time-to-treatment metrics from year one to year two, there was a statistically significant increase in first-door-to-puncture time (147 vs 159 minutes, p = 0.044), while the time from the EVT center door to puncture decreased (78 vs 70 minutes, p = 0.004); the onset-to-first-door (86 vs 87, p = 0.77) and onset-to-puncture times (271 vs 273, p = 0.47) did not vary with time. Appendix 2 (Appendix_02: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/15031/Appendix_02.pdf) shows data comparing patients with in-hospital vs. out-hospital stroke onset. In-hospital stroke patients were younger and had shorter onset-to-puncture times.

DISCUSSION

The study shows that (1) the EVT rate for the two years of the study period was 8.27/100 000 inhabitants/year, (2) the EVT rate increased from the first to the second year,

Table 1 – Median (IQR) times from onset to first door, first door to puncture and onset to puncture. Additional time metrics are presented distinguishing between patients transferred from a primary stroke center and primary admissions to EVT centers (non-transferred). The p-value presented represents the statistical significance of the Wilcoxon rank-sum tests comparing transferred with non-transferred patients. A statistically significant difference was assumed for p-values < 0.05.

Study Period	Total (n = 1542)		Transferred (n = 868)		Non-transferred (n = 674)		p
	Median [IQR]	missing	Median [IQR]	missing	Median [IQR]	missing	
Onset – 1 st door time	87 [60 - 142]	187	83 [56 - 129]	97	95 [64 - 156]	90	< 0.001
1 st door – puncture	155 [105 - 230]	54	211 [158 - 271]	40	107 [78 - 140]	14	< 0.001
Onset – puncture	260 [192 - 345]	177	308 [249 - 382]	80	208 [165 - 287]	97	< 0.001
EVT center door - puncture	73 [37 - 115]	50	43 [27 - 77]	36	107 [78 - 140]	14	< 0.001
Year 1	Total (n = 600)		Transferred (n = 299)		Non-transferred (n = 301)		
Onset – 1 st door time	87 [60 - 148]	73	83 [55 - 145]	35	90 [63 - 150]	38	0.048
1 st door – puncture	147 [94 - 228.5]	36	215 [164 - 279]	23	104 [73 - 140]	13	< 0.001
Onset – puncture	259.5 [180 - 347.5]	68	318 [260 - 390]	24	205 [160 - 289]	44	< 0.001
EVT center door - puncture	78 [43 - 118]	29	52 [29 - 86]	16	104 [73 - 140]	13	< 0.001
Year 2	Total (n = 942)		Transferred (n = 569)		Non-transferred (n = 373)		
Onset – 1 st door time	86 [60 - 137.5]	114	83 [58 - 124]	62	95 [65 - 161]	52	< 0.001
1 st door – puncture	159 [113 - 232]	18	209 [155 - 267]	17	107 [81 - 140]	1	< 0.001
Onset – puncture	260 [198 - 345]	109	301 [245 - 380]	56	213 [170 - 286]	53	< 0.001
EVT center door - puncture	70 [35 - 112]	21	40 [26 - 73]	20	107 [81.5 - 139.5]	1	< 0.001

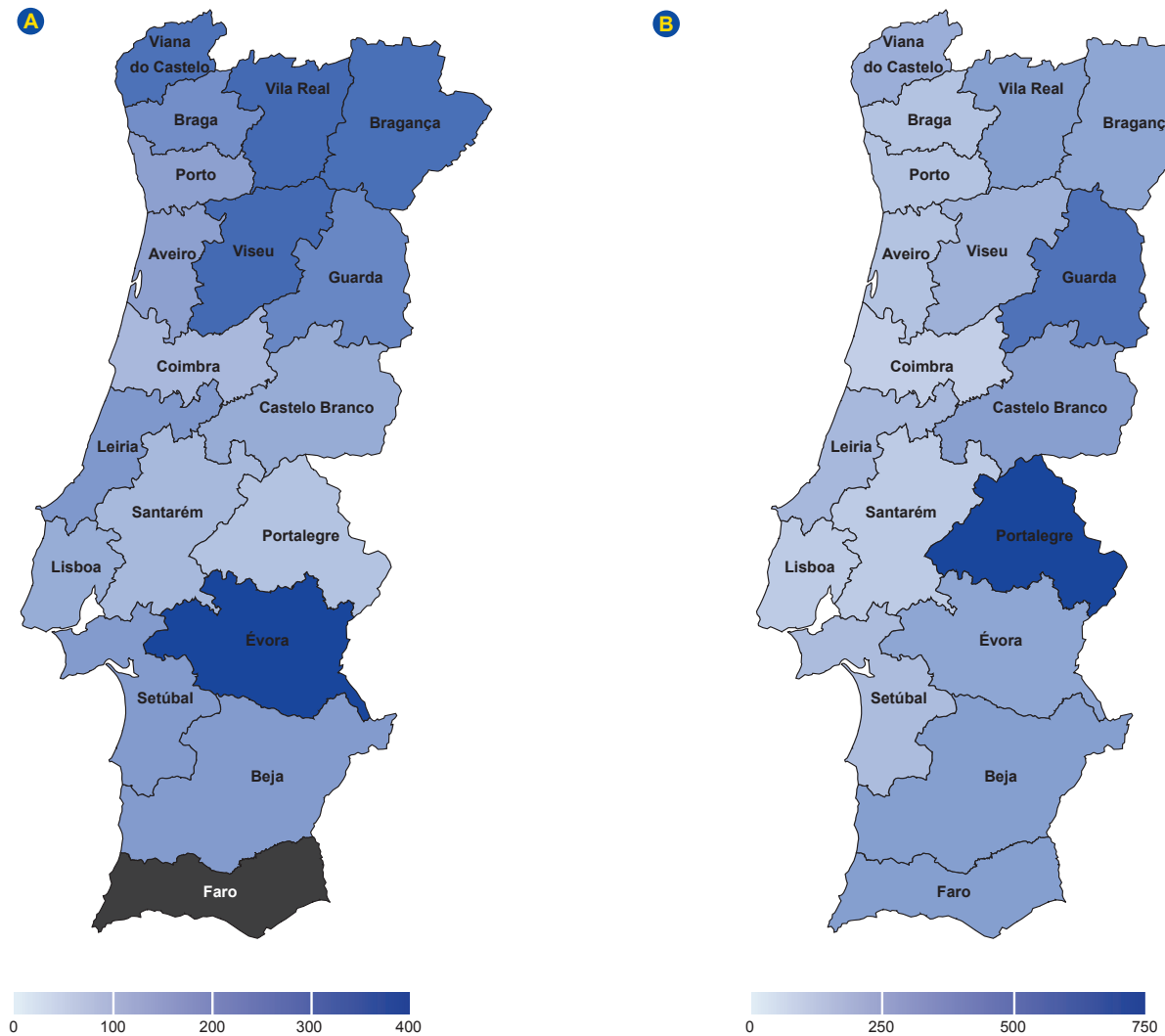


Figure 3 – (A) Median door-to-puncture times per district during the study's first year; (B) Median door-to-puncture times per district during the study's second year. Times are presented in minutes. Black shaded regions did not register any thrombectomy procedures

(3) EVT rates were markedly heterogeneous between regions (from 1.58/100 000/year to 16.53/100 000/year), and (4) there were regional differences in the time from stroke onset to puncture, with similar onset-to-first-door times.

Comparing our results to the available information regarding the number of acute ischemic strokes that could be potential EVT candidates, our national EVT rate matched the expected rate and is among the highest in Europe.⁹ Although the rate increase from the first to the second year likely reflects the effects of several factors, the authors highlight the fast learning and optimization processes that occurred after the efforts to implement a new treatment strategy. These efforts were sustained in subsequent years by creating National Reference Centers for Interventional Neuroradiology in Portugal, which led to further optimization of processes involving EVT.

Comparing our time metrics to those reported in EVT trials,⁵⁻⁸ we found slightly higher median stroke-onset-to-puncture times (272 min vs 200 - 269 min in EVT trials) but

similar door-to-puncture times for patients directly admitted to EVT centers (107 min vs 90 - 113 min in EVT trials). These differences likely reflect distinct time-based indications in a real-world setting and inter-hospital transfer delays. Moreover, the number of patients transferred to EVT centers increased from the first to the second year, which improved in-hospital time metrics, reflecting a continuous increase in EVT access.

We found a marked geographic heterogeneity in EVT rates and time metrics that follows the distribution of healthcare resources, with areas from the south and the inner country having poorer access to EVT than areas closer to EVT centers with more public resources. An improvement of the EVT's organization in Portugal must consider not only the travel time from remote areas to EVT centers but also strategies to optimize diagnosis and treatment decisions in primary stroke centers and improve inter-hospital transport. However, it must still ensure that EVT centers have enough case volume and expertise to provide safe and high-quality

EVT.

Our survey's major strengths are that all Portuguese EVT centers participated in the study and the data were collected from the prospective stroke registries at each center by experienced stroke physicians. Another strength is that our results are adjusted to age and each district's population.

The study limitations include the assumption of the patient's address as the location of stroke occurrence, as some patients may have been at other locations when the stroke occurred. Moreover, regional stroke incidence was not studied because this data was not available for analysis. Despite the relevance of this limitation, considering the geographically small country analyzed (Portugal), and the fact that different regions share a common genetic background, it seems reasonable to expect that the statistical adjustment for the population's size and age would likely limit this potential bias.

It should also be pointed out that medical, social, and economic factors may also contribute to regional heterogeneity in treatment access, and these variables were not available for analysis. Furthermore, regarding time differences, EVT logistic and chain of care protocols are heterogeneous across different centers. Therefore, our results should be interpreted with these limitations in mind. Additional limitations include insufficient time metrics to precisely identify bottlenecks in terms of access to EVT and the absence of outcome measures, such as post-EVT functional status, which were outside of this survey's scope. Moreover, patients might have been treated more than once (different events), but each admission was considered independently.

CONCLUSION

The overall national rate of EVT in the first two years after the organization of EVT-capable centers is one of the highest among European countries. Moreover, stroke-onset-to-first-door times and in-hospital procedural times in the EVT centers were comparable to those reported in the randomized controlled trials performed in high-volume tertiary hospitals. However, there are still significant regional disparities in terms of access and inter-hospital transit times that require improvements.

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AUTHORS CONTRIBUTION

MCD, RSR: were responsible for the writing of the first draft of the manuscript.

MCD, RSR, APN, PF, BM, IF, JR, JRL, LC, GS, EM, DG, RF, HM, AC, MC, LMV, PB, TG, AC, MR, PT, LN, TPM, PC, JPF, GM, EA, MLS, ECC, GO, LP, LN, MR, JPM, SC, FG, GB, TB, JR, CF, JP, JMA, JMA, JSF: collected the data.

JVS, RMN, JV, ML, AF: conducted the statistical analyses.

VTC, JSF, JCL: were responsible for the idea and design of the study and critically reviewed the final version of the manuscript.

All authors contributed to the writing of the manuscript and reviewed the final manuscript.

DATA AVAILABILITY STATEMENT

The dataset generated for this study can be made available by the corresponding author after reasonable request and for research purposes.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

Patients were not directly studied, and their informed consent was not deemed necessary because the data collected was retrospective and immediately anonymized.

COMPETING INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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