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Are there socio-economic inequities in access to reperfusion therapy: The Stroke 69 cohort

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Abstract

Background and Purpose. Low socio-economic status of individuals has been reported to be associated with a higher incidence of stroke and influence the diagnosis after revascularization. However, whether it is associated with poorer acute stroke management is less clear. To determine whether social deprivation was associated with a poorer access to reperfusion therapy, either intravenous thrombolysis (IVT) and/or endovascular thrombectomy (EVT) in a population-based cohort.

Methods. Over a 14-month period, all consecutive adult patients admitted to any emergency department or a comprehensive or primary stroke center (CSC/PSC) of the Rhône county with a confirmed ischemic stroke were included. The socioeconomic status of each patient was measured using the European Deprivation Index (EDI). The association between EDI and access to reperfusion therapy was assessed in univariate and multivariate logistic regression analyses.

Results. Among the 1226 consecutive IS patients, 316 (25%) were admitted directly in a PSC or CSC, 241 (19.7%) received a reperfusion therapy; 155 IVT alone, 20 EVT alone, and 66 both therapies. Median age was 79 years, 1030 patients had an EDI level of 1 to 4, and 196 an EDI of 5 (the most deprived group). The most deprived patients (EDI level 5) did not have a poorer access to reperfusion therapy compared to all other patients in univariate (OR 1.22, 95%CI [0.85; 1.77]) nor in multivariate analyses (adjOR 0.97, 95%CI [0.57; 1.66]).

Conclusions. We did not find any significant association between socioeconomic deprivation and access to reperfusion therapy. This suggests that the implementation of EVT was not associated with increased access inequities.

Key Words: Social Deprivation; Stroke; Reperfusion; Thrombolytic Therapy; Thrombectomy; Cohort Study

Clinical Trial Registration:

<https://clinicaltrials.gov/ct2/show/NCT02596607?term=NCT02596607&rank=1>.

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1. Introduction

Stroke is the third-leading cause of death and the leading cause of long-term neurological disability in the world (1,2). In France, stroke represents 130 000 new cases per year, 80% of which are ischemic strokes (IS) (3). Despite the availability of intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT), access to these reperfusion therapies is often sub-optimal (4,5). Although patients have better outcomes when they receive the most recent evidence-based care, there are still geographical inequities regarding implementation of this care (6). In addition, Clua-Espuny et al. reported that age, gender and comorbidities, influenced the prognosis after revascularization (5), which suggests that these factors should be included in the decision process of reperfusion therapy. A wide variety of other factors may influence access to reperfusion therapy. These may be associated with resource organization (e.g. geographic accessibility to primary or comprehensive stroke centers (PSC/CSC) (7,8), efficiency of transportation, structural organization), patients (age, comorbidities, gender (9,10)) or their stroke's characteristics (e.g. tissue window (11), functional status before stroke, severity). In addition, inequities in access to reperfusion therapies may be associated with socioeconomic status (SES) as it is often correlated with health literacy that may cause delays regarding the proper use of the healthcare system (12).

Social inequalities in health, in particular regarding disability, death or illness, are well known; they are often linked to education, income and housing tenure, and vary across different geographical areas (13). A low SES has been correlated with higher incidence of stroke, access to health service after stroke and mortality (14–16). However, its potential influence on pre-stroke management remains more controversial (17–25). Furthermore, published most studies relied on data gathered before 2010 and thus concerned access to IVT only. Finally, it has been shown that existing equity intervention frameworks often lack specific guidance for implementing organizational change, and this may be the case for EVT implementation (26). As reperfusion therapy has recently greatly improved with the implementation of thrombectomy, the existence of inequalities in access is yet unclear. We hypothesized that a set of SES factors related to the patient and his/her living environment could have an impact on access to a reperfusion therapy. The aim of the present study was therefore to measure the

association between SES and access to acute IS therapy administration (IVT and/or EVT) over a more recent period with a larger implementation of EVT within a population-based cohort study.

2. Methods

2.1 Study design, setting and participants

Reported herein is an ancillary study of the STROKE69 population-based cohort that included all adult patients aged 18 years or older with a suspicion of acute stroke admitted to an emergency department (ED), a PSC, or a CSC of the Rhône County between November 6, 2015 and December 31, 2016. Definitive diagnosis was based on cerebral imaging by computed tomography scan and/or magnetic resonance imaging (MRI), and confirmed by a neurologist. In the present study, only STROKE69 study patients' resident in the Rhône county, and not admitted to intensive care were included. The Rhône county has a population of 1,821,995 inhabitants (*Institut national de la statistiques et des études économiques, Insee*), *i.e.* 560.8/km², there are 7 EDs, one CSC in Lyon and one PSC in Villefranche-sur-Saone. The study was approved by the national commission on data protection (*CNIL*), and the ethics committee according to national procedures in place at the time of the study.

2.2 Variables

The primary outcome was administration of reperfusion therapy, either IVT and/or EVT. A DAG method was carried out through a literature search, consideration of confounding factors (organizational and resources' factors, patients and stroke's characteristics) and exchange between experts in order to identify the relationships between the variables. We then choose that the exposure of interest was the European deprivation index (EDI) a proxy for SES developed by Pernet *et al.* in 2012 (27) and validated in France and four other European countries (28). It is an ecological deprivation index associated with the place of residence of individuals designed to measure social precariousness based on socio-economic variables. The multivariate logistic regression used to develop the EDI selected 10 variables: education, overcrowded housing (more than 1 person per room), heating, access to a car, nationality (foreign or French nationality), occupational classes, household types (single-parent household or pensioner, couple with or without child, without family), number of persons in the household, employment status, and tenure (owner/renter) (Appendix 1). Data used for the French EDI calculation were extracted from the national institute for statistics database (Insee, 2014). The *IRIS (Ilots Regroupés pour l'Information Statistique)* are the smallest geographical census units

available in France. *IRIS* was identified by the postal address systematically collected for each patient in the cohort. Each *IRIS* is globally homogeneous regarding social characteristics. As recommended we calculated an EDI score for each of the 769 *IRIS* of the Rhône County in 5 classes from 1 (the least deprived) to 5 (the most deprived) using ArcGIS 10.5.1 software (Environmental Systems Research Institute [ESRI]-GIS Mapping Software, Solutions, Services, Map Apps, and Data Inc., Redlands, CA, USA).

2.3 Data sources

Data were collected from the medical records filled within the STROKE69 cohort study. These were final diagnosis (IS, hemorrhagic stroke, or other diagnosis), age, sex, cardiovascular disorders (myocardial infarcts, heart failure, rhythm disturbances), history of stroke or transient ischemic attack (TIA), time of symptom onset, call to emergency call center (ECC, #15), means of transport, place of first admission, stroke severity (National Institute of Health Stroke Scale – NIHSS), cerebral imaging, EVT and/or IVT, and pre- and in-hospital management times. Travel time from place of first symptoms to first admission was modelled from the road network and speed limit data using the ArcGis 10.5.1. *Network Analyst* extension.

2.4 Statistical methods

Quantitative data were described using mean and SD or median and quartiles 1 and 3 (Q1-Q3) depending on their distribution. Qualitative data were described using numbers and frequencies. EDI was dichotomized in two groups, the most deprived (EDI level 5) versus all other EDI levels (1-4) since the most deprived group has been shown to be at higher risk of poor access to care (22). Comparisons between the two groups (deprived Y/N) were carried out using Student-t test or the non-parametric Wilcoxon sum-rank test depending on their distribution for quantitative characteristics, and Chi-squared test or Fisher's exact test for qualitative characteristics. Logistic regression models were constructed with access to reperfusion therapy (Y/N) as the dependent variable. Univariate analyses were conducted and a multivariate model was performed with the EDI level as the exposure of interest, controlling for potential confounders with $p < 0.20$ (sex, age, history of stroke and/or TIA, cardiovascular disorders, admission during non-working hours, severity (NIHSS score), place of first admission, estimated travel time from place of first symptoms to first admission, and time from symptoms to imaging). Given the non-normal distribution of the variable, missing values for time from symptoms to imaging were imputed by the median value of data available; sensitivity analyses without missing data were conducted (in univariate and multivariate). In order to check the

predictive capacity and the goodness-of-fit, we performed adequacy test of the logistic multivariate model (discrimination with c-stats and Hosmer-Lemeshow test). Interaction between exposure of interest and other covariates were tested and we did not find any statistically significant interaction. All analyses were two-sided, significance was set to a $p < 0.05$. Analyses were carried out using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

3. Results

Of the 3 442 patients screened for a suspected stroke in STROKE69 cohort, 1543 had a confirmed diagnosis of IS, of whom 1226 were included (Figure 1), and 241 (19.7%) received a reperfusion therapy (155 IVT alone, 20 EVT alone, and 66 both).

Among the study population ($n=1226$), 51.1% were female (Table 1). Median age at stroke was significantly lower among deprived patients. The number of patients in each class of EDI was: Q1 ($n=278$, 22.8%), Q2 ($n=276$, 22.5%), Q3 ($n=252$, 20.5%), Q4 ($n=223$, 18.2%) and Q5 ($n=196$, 15.9%). Regarding outcomes, there was no significant difference in management times nor in the proportion of patients receiving reperfusion therapy. There was a trend towards a greater proportion of deprived patients who had a stroke that occurred in the street or public place (10.6% vs. 5.9%, $p=0.06$), first admitted to PSC or CSC (4.1% vs. 2.8% for PSC, and 28.1% vs. 21.8% for CSC, $p=0.08$), and having access to MRI (34.2% vs. 28.7%, $p=0.15$). Figure 2 presents the distribution of IS patients according to their EDI in the Rhône county.

In univariate analyses, age (crude OR 0.88, 95%CI [0.84-0.92]), stroke or TIA history (crude OR 0.73, 95%CI [0.53-0.99]), stroke severity (crude OR 10.29, 95%CI [6.08-17.41] for severity score >20 and OR 5.06, 95%CI [3.18-8.05] for severity score between 15-20), and modality of first admission (crude OR 16.85, 95%CI [11.88-23.90] for CSC and 28.49, 95%CI [13.66-59.43] for PSC) were significantly associated with access to reperfusion therapy and were introduced to the multivariate model. In the latter ($n=1189$), the group that received reperfusion therapy had a more severe stroke (adjOR 6.88, 95%CI [3.35; 14.13] for NIHSS >20), and was more frequently directly admitted in a CSC or a PSC (adjOR 7.30, 95%CI [2.92; 18.25] and adjOR 6.04, 95%CI [3.87; 9.43], respectively). Patients had less chance to get reperfusion therapy when they had a stroke history (adjOR 0.51, 95%CI [0.30; 0.86]), cardiovascular disorder (adjOR 0.56, 95%CI [0.36; 0.89]) or when they had a longer time from symptom onset to imaging (adjOR 0.99, 95%CI [0.99; 0.99]). There was no significant association between deprivation level and access to reperfusion therapy after adjusting for potential confounders (adjOR 0.97 95%CI [0.57; 1.66]; Table 2). The logistic model with imputation of missing data

showed good predictive capacity; c-stat=0.93, Hosmer-Lemeshow test p=0.45. Similar analyses were performed without imputation of missing data and this is not changing the results (Appendix 2).

4. Discussion

We found that access to reperfusion therapy was not different in the most deprived IS patients (18.3%) vs. the other IS patients (15.4%) even after adjusting for confounding factors. Although there is strong evidence that low SES is associated with increased incidence of cardiovascular diseases and stroke, the possible association between SES and the efficacy of stroke management is less clear. Four studies found that patients with low SES were less likely to receive IVT (17,21,24,25) and three other studies found no association between SES and access to IVT (18,22,23). As IVT and EVT need different equipment and resources (IVT may be performed in ED) accessibility to EVT may have somehow different determinants. Only two studies considered also EVT. One conducted in USA in 2006-2010 found a lower SES was associated with a poorer access to EVT (24). The other, conducted in Sweden in 2003-2009 found only in non-university hospitals low education significantly associated with poorer access to reperfusion (17). Several factors could explain our results. Firstly, these two studies relied on data gathered before 2010 before efficacy of this treatment was acknowledged by large clinical trials and in national guidelines (29,30). Secondly, in the American study, SES was measured at the individual level, based on ethnicity, income level and health insurance whereas we estimated SES by an ecological approach. Additionally, our system of universal health insurance is quite different from that of USA. Thirdly, the Swedish study found lower SES was associated with poorer access to reperfusion only in non-university hospitals whereas in the Rhône County IS patients were mostly managed in the large University hospital of Lyon.

Strengths and Limitations

The choice of a community-based indicator instead of an indicator measured at the individual level may be considered as a limitation. Individual indicators are more accurate as it is likely incomes and levels of education may vary within a same neighborhood. Consequently, an area-based measurement tool for deprivation may lead to an ecological bias, *i.e.* the misclassification of some individuals in a geographical area, which does not exactly represent the actual SES of the individuals (31). However, ecological indexes have been used and validated to describe social inequities in general health service access (32). It also highlights the availability of community resources and considers aspects of the patient's environment that can influence health. Finally, as these indicators are easily available for each patient it would be possible to

analyze large representative population-based cohorts to prevent selection bias. The EDI ecological index used herein was developed and validated in France and subsequently extended to four European countries (28,33,34). It takes into account the multidimensionality of socioeconomic characteristics and assumes that inequities are related to social and environmental influences and not only to behavioral individual factors. It is easy to estimate and provides complete high-quality data for the entire study population. Social inequalities in health are in fact, generally geographical and people with similar profiles tend to group together in an identical place. Furthermore, one of the studies conducted on access to IVT measured SES both at the individual (ethnicity) and geographical level and found similar results for the two indicators (22).

The main strength of our study is that it was population-based, including all patients hospitalized in the County with an acute IS, and relied on more recent data than other studies, which is of particular importance in view of the recent implementation of EVT. These results are representative of the Rhône County, nevertheless it is difficult to assert that they would be exactly similar in other areas of France with different geographical organization of the strokes unit/centers. Yet guidelines are issued at the national level and the organization of transportation in connection with the ECC (#15) is somehow standardized over the whole country, which probably avoids too large differences between areas. Finally, these results could be different from other countries with very different organization of care, notably regarding cost and insurance coverage and also territorial organization.

5. Conclusion

These results suggest that the organization of the acute care pathway for patients with IS in France, and particularly the implementation of EVT is not associated with increased access inequities as it seems similarly effective regardless of the level of social disadvantage.

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8. Conflict of interest

Declaration of interest: none.

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Table 1. Characteristics of patients according to deprivation level

	Total n=1226	EDI level 1 to 4 n=1030	EDI level 5 n=196	p-value
Female, n (%)	626 (51.1)	532 (51.7)	94 (48.0)	0.34
Age (median, [Q1-Q3]; years)	79 [67-86]	80 [68-87]	73 [62-84]	<0.0001**
Medical history, n (%)				
Stroke and TIA	291 (23.7)	252 (24.5)	39 (19.9)	0.17
Cardiovascular disorders	408 (33.3)	346 (33.6)	62 (31.6)	0.59
NIHSS score, n (%) (n=1214)				
0 – 4	571 (47.2)	478 (47.0)	93 (48.0)	
5 – 14	434 (35.9)	367 (36.1)	67 (35.1)	
14 – 20	126 (10.4)	110 (10.8)	16 (8.4)	
>20	78 (6.5)	63 (6.2)	15 (7.9)	
ECC call, n (%)	761 (62.1)	629 (61.1)	132 (67.4)	0.10
Admission during non-working hours, n (%) (n=1225)	667 (54.5)	557 (54.1)	110 (56.1)	0.61
Provenance, n (%) (n=1058)				
Home	911 (86.5)	776 (86.9)	135 (84.4)	
Medical center / Healthcare institution	72 (6.8)	64 (7.2)	8 (5.0)	
Street or public place / other	70 (6.7)	53 (5.9)	17 (10.6)	
Means of transport, n (%) (n=1099)				
Mobile emergency unit	34 (3.1)	31 (3.4)	3 (1.7)	
Ambulance	327 (29.9)	283 (30.8)	44 (25.1)	
Fire service	587 (53.6)	485 (52.7)	102 (58.3)	
Private/own/other	147 (13.4)	121 (13.2)	26 (14.9)	
Place of first admission, n (%)				
Emergency department	910 (74.2)	777 (75.4)	133 (67.9)	0.08
PSC	37 (3.0)	29 (2.8)	8 (4.1)	
CSC	279 (22.8)	224 (21.8)	55 (28.1)	
Cerebral imaging in the 24 hours after admission, n (%) (n=1211)				
CT	753 (62.2)	645 (63.6)	108 (55.1)	0.15
MRI	358 (29.6)	291 (28.7)	67 (34.2)	
Both	96 (7.9)	76 (7.5)	20 (10.2)	
None	4 (0.3)	3 (0.3)	1 (0.5)	
Estimated travel time median, [Q1-Q3]; minutes (n=1223)	15.1 [10.0-20.1]	15.1 [10.2-20.3]	14.6 [9.1-19.3]	0.31

Intra-hospital management times, median [Q1-Q3]; minutes				
Door to imaging (n=1136)	118 [36-236]	116 [36-237]	127 [35-227]	0.89
Symptom to PSC/CSC (n=526)	230 [102-520]	234 [103-510]	212 [90-723]	0.92
Symptom to imaging (n=815)	243 [125-513]	241 [128-492]	247 [120-612]	0.80
Door to needle † (n=211)	56 [33-78]	54 [31-79]	59 [38-76]	0.26
Access to Reperfusion therapy, n (%)	241 (19.7)	197 (19.1)	44 (22.5)	0.28

CT: Computed Tomography; ECC, Emergency Call Center; EDI: Ecological Deprivation Index (most deprived: EDI 5); MRI: Magnetic Resonance Imaging; NIHSS, National Institute of Health Stroke Scale Q1-Q3: Quartiles 1 and 3; SD: Standard Deviation; TIA: Transient Ischemic Attack.

† Needle means thrombolysis and/or endovascular thrombectomy.

*Significant association

Table 2. Multivariate analysis of factors associated with access to reperfusion therapy (with imputation of missing data)

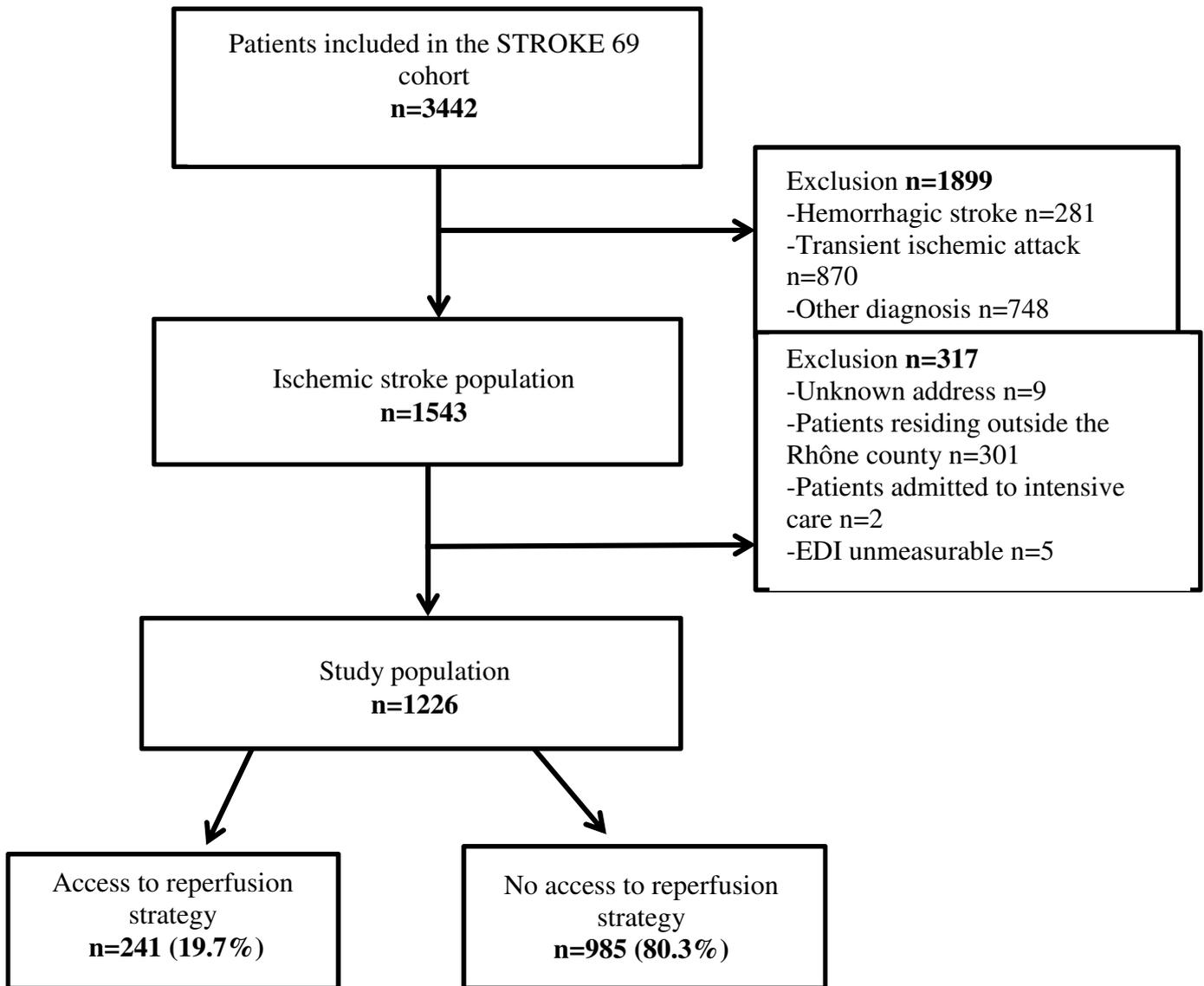
	Reperfusion therapy n=241	No reperfusion therapy n=985	Crude OR [95% CI]	Adjusted OR † [95% CI] (n=1189)
Female, n (%)	114 (47.3)	512 (52.0)	0.83 [0.63;1.10]	1.39 [0.91;2.12]
EDI level, n (%)				
Least deprived (levels 1 to 4)	197 (81.7)	833 (84.6)	ref	ref
Deprived (level 5)	44 (18.3)	152 (15.4)	1.22 [0.85; 1.77]	0.97 [0.57;1.66]
Age (years), median [Q1-Q3]	74.0 [62.0-83.0]	80.0 [68.0-87.0]	0.88 [0.84;0.92] ‡	0.88 [0.82;0.95] ‡
History of stroke and/or TIA, n (%)	31 (12.9)	260 (26.4)	0.41 [0.28; 0.62]	0.51 [0.30;0.86]
Cardiovascular disorder, n (%)	67 (27.8)	341 (34.6)	0.73 [0.53; 0.99]	0.56 [0.36;0.89]
Admission during non-working hours, n (%)	135 (56.0)	532 (54.1)	0.92 [0.70; 1.23]	0.88 [0.58;1.33]
Stroke severity, n (%) (n=1209)				
0 – 5	53 (22.2)	518 (53.4)	ref	ref
5 – 14	103 (43.1)	331 (34.1)	3.04 [2.12; 4.35]	4.07 [2.49;6.64]
15 – 20	43 (18.0)	83 (8.6)	5.06 [3.18; 8.05]	5.44 [2.81;10.53]
>20	40 (16.7)	38 (3.9)	10.29 [6.08; 17.41]	6.88 [3.35;14.13]
Place of first admission, n (%)				
Emergency department	62 (25.7)	848 (86.1)	ref	ref
PSC	25 (10.4)	12 (1.2)	28.49 [13.66; 59.43]	7.30 [2.92;18.25]
CSC	154 (63.9)	125 (12.7)	16.85 [11.88; 23.90]	6.04 [3.87;9.43]
Time from Symptoms to imaging (minutes), median [Q1-Q3] (n=815)	109 [86-145]	345 [191-602]	0.99 [0.98;0.99]	0.99 [0.99;0.99]
Estimated Travel time (minutes), median [Q1-Q3] (n=1223)	17.0 [12.2- 23.3]	14.5 [9.2- 19.2]	1.03 [1.01;1.04]	1.02 [0.99;1.05]

CI: Confidence Interval; CSC: Comprehensive Stroke Center; EDI: Ecological Deprivation Index; OR: Odds Ratio; PSC: Primary Stroke Center; Q1-Q3: Quartiles 1 and 3; TIA: Transient Ischemic Attack.

† OR adjusted for sex, age, severity in class, deprivation in class, place of first admission, admission during travel time, cardiovascular disorders, history of stroke and/or TIA, time

from symptoms to imaging and estimated travel time.
‡ Odds Ratio for 5 years.

Figure 1. Study flow chart



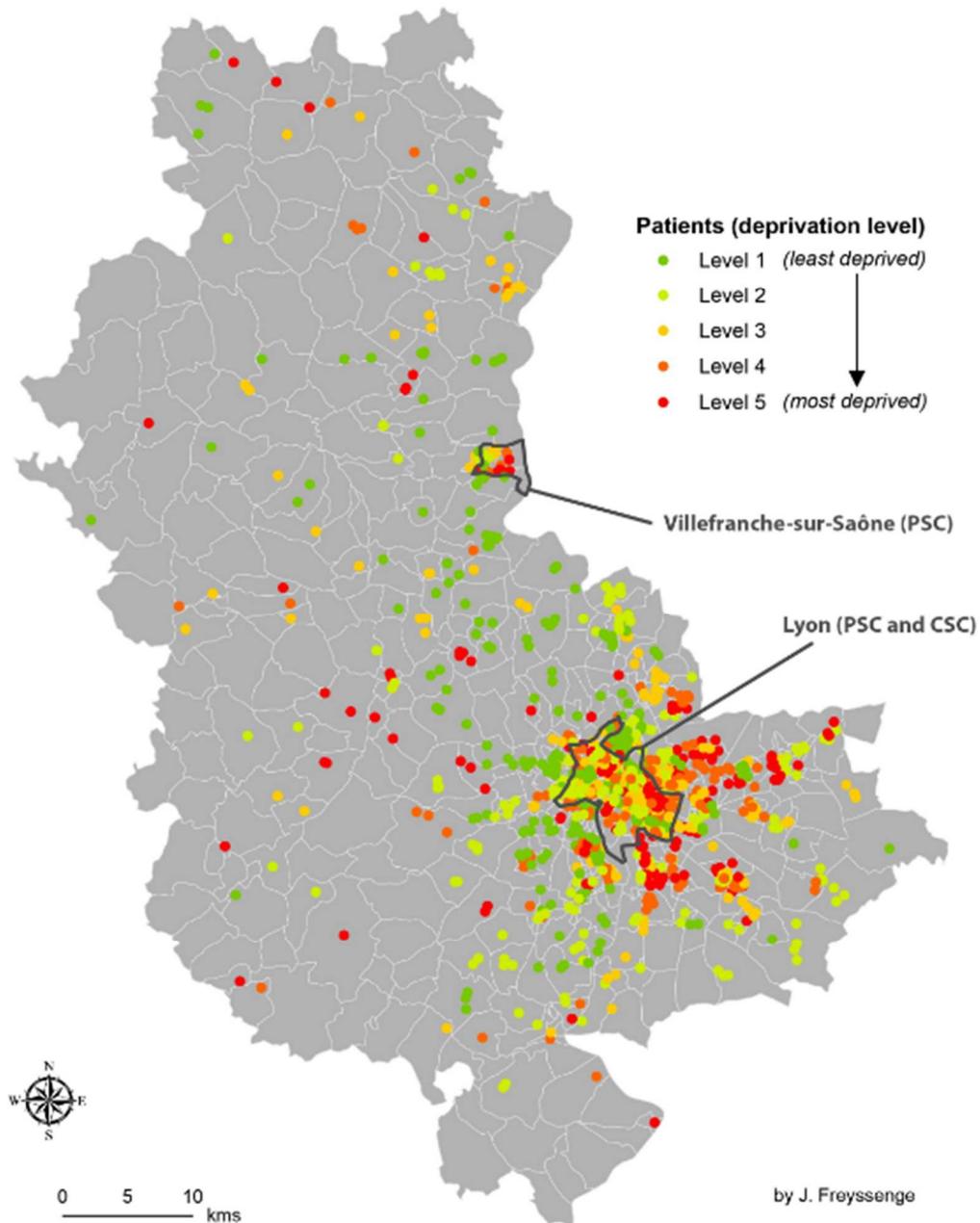


Figure 2. Geographic distribution of the 1226 acute IS patients' address of residence into the Rhône County. The ecological deprivation index (EDI) was used to measure social deprivation. Lyon and Villefranche-sur-Saône are the two main cities of the Rhône County with, respectively, PSC (Primary Stroke Center) and CSC (Comprehensive Stroke Center) and only PSC