Neighbourhood Deprivation, Distance to the Nearest Comprehensive Stroke Centre, and Access to Endovascular Thrombectomy for Ischemic Stroke: a Population Based Study

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Background:

Endovascular thrombectomy (EVT) has revolutionized ischemic stroke care. However, it is available primarily at comprehensive stroke centres (CSCs). Individuals from deprived neighbourhoods or rural locations may have less access to EVT. This work investigated whether individuals living in more deprived neighbourhoods are less likely to be treated with EVT and whether this relationship is mediated by the distance an individual lives from the nearest CSC.

Methods:

We performed a retrospective study including all individuals from Alberta, Canada who were treated with Alteplase for an ischemic stroke between January 1, 2017, and December 31, 2019. The primary outcome was treatment with EVT. Neighbourhood deprivation was assigned based on the Pampalon Index. Distances to the nearest CSC were calculated based on participant postal codes. We used logistic regression modeling to assess for a relationship between our dependent and independent variables. We performed a mediation analysis to calculate the Average Causal Mediation Effect (ACME) of distance to the nearest CSC on the relationship of interest.

Results:

Patients from the most deprived neighbourhoods were less likely to be treated with EVT in the primary model (OR 0.43, 95% CI: 0.24 – 0.77). Neighbourhood deprivation was not significantly associated with EVT when distance to the nearest CSC was included as a covariate. The calculated ACME was -0.059 (95% CI: - 0.082 - -0.030) indicating statistically significant mediation by distance to the nearest CSC.

Conclusions:

These results suggest that individuals from more deprived neighbourhoods are less likely to be treated with EVT and that improving access to individuals from rural locations may improve the equitable distribution of EVT.

Introduction

Acute ischemic stroke is the most common form of cerebrovascular disease and typically results from the sudden occlusion of a cerebral artery.[1] This leads to tissue ischemia and subsequent neural injury, which progresses to irreversible cell death rapidly with time.[1] Unfortunately, ischemic stroke remains a leading cause of morbidity and mortality worldwide.[2] Early treatment goals are centered around reperfusing the ischemic brain, which was traditionally accomplished by administration of intravenous thrombolytic medications within 4.5 hours of stroke onset.[3] More recently, endovascular thrombectomy (EVT) for ischemic stroke has revolutionized the treatment of this condition.[4-10]

Multiple randomized controlled trials were published in 2015 and demonstrated that EVT, in addition to intravenous (IV) thrombolysis, was superior to IV thrombolysis alone in preventing death and disability after ischemic stroke. [4-10] Because the injury from tissue ischemia progresses to irreversible cell death quickly, EVT is best performed within 6 hours of stroke onset as it reperfuses the ischemic brain and prevents further progression of the cell death.[11,12]

EVT for ischemic stroke is resource intensive and is only available at comprehensive stroke centres (CSCs). Several studies using the American National Inpatient Sample (NIS) database have found an association between geographic markers of socioeconomic status (SES) and the odds of being treated with EVT.[13-16] However, this question has not been assessed in the context of Canada’s healthcare system. Unlike the United States, Canada has a publicly funded, universal healthcare system. The Canada Health Act (1984) stipulates that every Canadian province must provide comprehensive, universal, and accessible hospital services to all residents.[17] Individuals who would have a financial barrier to care in a private insurance system, theoretically, have no such barrier in Canada.

Measuring patient SES in retrospective studies poses challenges. In Canada, the most widely used measure of neighborhood SES was developed by Pampalon and colleagues.[18,19] They created an area-based metric for assessing material and social deprivation. Scores were based on the smallest geographical unit collected on the Canadian census: the dissemination area (DA).[20] While this Material and Social Deprivation Index (MSDI) was initially created for the province of Quebec alone, it has since expanded to cover the whole of Canada and has previously demonstrated an association with mortality after stroke.[21,22]

We assessed whether an individual's neighborhood SES (as estimated by their Pampalon index) is predictive of their access to EVT after receiving Alteplase when suffering an ischemic stroke among patients living in Alberta, Canada. A secondary aim was to assess whether any discrepancy in the odds of receiving EVT is mediated by the distance an individual lives from the nearest CSC. We hypothesize that individuals from low SES areas of Alberta will be less likely to receive EVT after Alteplase for ischemic stroke. However, we anticipate that this relationship is, at least partially, explained by the association between low SES neighborhoods and the distance they are situated from CSCs.

Methods

Data and Population

We performed a retrospective analysis of the "Quality Improvement and Clinical Research" (QuICR) database. This is a prospective dataset including all patients treated with intravenous thrombolysis and/or endovascular thrombectomy for ischemic stroke in Alberta and is maintained by the Cardiovascular and Stroke Strategic Clinical Network at Alberta Health Services.[23] We included all individuals greater than 18 years of age, living in Alberta, who were hospitalized with an ischemic stroke and treated with IV alteplase between January 1, 2017 and December 31, 2019. Clinical and demographic characteristics of our patient population were extracted from the QuICR and the Alberta Health Services "Data Integration, Measurement, and Reporting" (DIMR) administrative databases.[24]

Independent Variable of Interest

Material and Social Deprivation

We linked patient home address postal codes to the federal census dissemination areas (DAs) within the province of Alberta.[25] We assigned a material and social deprivation score to each DA using data provided by the Institut National de Santé de Québec.[26] These metrics have been previously validated for use across Canada.[27] Scores were grouped into quintiles for both material and social deprivation, from least deprived (most privileged) to most deprived. These were combined to create an overall measure of deprivation for use in the statistical analysis. The two quintiles were combined based on the suggested method by Garnache *et al.* (Figure 1).[26]

Outcome of Interest:

The primary outcome of this study was treatment with EVT after receiving IV Alteplase for an individual's ischemic stroke. All individuals who had an EVT attempted were deemed to have been treated with EVT, regardless of whether the vessel was opened successfully with the intervention.

The secondary outcome of this work was the Average Causal Mediation Effect (ACME) between treatment with EVT and the distance from an individual's postal code (in kilometers) to the nearest CSC. This metric provides an estimate of what portion of the discrepancy in odds of being treated with EVT based on neighborhood SES is attributable to the distance from the neighborhood to the nearest CSC. We performed our mediation analysis according to the steps outlined by Baron and Kenny (1986).[28]

Distance to the Nearest CSC

We examined the home address postal codes for all patients in the dataset to ensure they were residents of Alberta, Canada. We calculated distances, in kilometers, from the centre of each postal code to the nearest CSC in Alberta (University of Alberta Hospital in Edmonton and Foothills Medical Centre in Calgary) using ArcGIS Pro for geocoding and the NAD 83 UTM 11 map projection (Esri. Redlands, Ca, USA). We examined the relationship between distance to the nearest CSC and neighborhood deprivation using a multinomial logistic regression model.

<u>Statistical Analysis</u>

We used descriptive statistics to examine the baseline characteristic of the study cohort. Continuous variables that followed a normal distribution were assessed for an association with the outcome of interest using Student's t-test and categorical variables were assessed using Pearson's Chi-Squared test. Continuous variables that showed significant deviations from normality were assessed using non-parametric tests, as appropriate. To assess the relationship between our independent variables of interest and our primary outcome, we fit three multiple logistic regression models. All covariates for the model were selected *a priori* based on clinical relevance. In the first model, we included age, sex, and pre-Alteplase National Institute of Health Stroke Scale (NIHSS) score as covariates. The NIHSS score is a numerical marker of stroke severity, with higher numbers being indicative of a more severe stroke.[29] In a secondary model, we included distance to the nearest CSC as a covariate. We also included age and distance as potential effect modifiers using interaction terms and tested for significant effect modification using the Wald test. Lastly, we performed a formal mediation analysis using the mediate function from the *mediation* r package.[30] We calculated the ACME using the primary and secondary logistic regression models and specified distance to the nearest CSC as the mediating variable. We used a bootstrapping method with 500 simulations. We performed all modeling using a complete case analysis.

Statistical significance was set at $p = 0.05$. All statistical analysis was performed using R Studio (R Studio. Boston, MA, USA).

Results

There were 1400 individuals who suffered an ischemic stroke and were treated with intravenous alteplase in Alberta between January 1, 2017, and December 31, 2019. Of these, 65 were residents of other provinces or countries, and were excluded from the analysis, leaving 1335 patients in the study. Of the 1335 patients included, 314 (23.5%) had an EVT attempted, and 181 (13.6%) had missing data, excluding them from the analysis. Other characteristics of the study cohort can be seen in Table 1.

Distance to the Nearest CSC and Deprivation

We observed a statistically significant relationship between deprivation level and distance to the nearest CSC using a Kruskal-Wallis test (p = 0.002). In the multinomial logistic regression model, we observed a statistically significant difference in the odds of being in the most deprived neighborhood, as compared to the least deprived neighborhood, based on the distance an individual lives from the nearest CSC (OR 1.006, 95% CI: 1.004 – 1.009) (Figure 2).

Association between EVT and level of deprivation

We observed a statistically significant relationship between an individual's geographic deprivation level and treatment with EVT after Alteplase for ischemic stroke using a Kruskal-Wallis test (p = 0.04) (Figure 3). Bivariate logistic regression also demonstrated a statistically significant relationship between being in the most deprived deprivation level (i.e., level 5) and being treated with EVT after Alteplase for ischemic stroke (Table 2). The unadjusted odd ratio compared to the least deprived group of patients was 0.53 (95% CI 0.32 – 0.87).

We did not observe any evidence of significant effect modification using the Wald test ($p >$ 0.05). As such, the regression models did not contain any interaction terms. In the primary logistic regression model individuals from the lowest SES neighborhoods were significantly less likely to be treated with EVT than individuals from the highest SES neighborhoods (OR 0.431, 95% CI: 0.240 – 0.769)) (Table 3). The predicted proportion of patients who would receive EVT decreased with increasing distance to a CSC, regardless of neighborhood deprivation level (Figure 4). In the secondary model, neighborhood SES was not significantly associated with the odds of receiving EVT, though there was a significant inverse relationship between the distance an individual lives from a CSC and the odds of receiving EVT (Table 4).

<u>Mediation Analysis</u>

The mean ACME of distance to the nearest CSC across all deprivation levels was -0.059 (95% CI: - 0.082 - -0.030), which suggests statistically significant mediation by the distance an individual lives to the nearest CSC on the relationship between neighborhood deprivation and treatment with EVT.

Interpretation

The results of our unadjusted analysis imply that individuals who live in the most deprived areas of Alberta may be less likely to be treated with EVT after Alteplase for an ischemic stroke. However, the distance an individual lives from the nearest CSC accounts for much of this discrepancy, as demonstrated by our secondary model and mediation analysis. These findings suggest that the healthcare providers are not systematically excluding individuals from low SES neighborhoods from this novel treatment, which is encouraging. Nonetheless, disparities may persist. Low SES neighborhoods tend to be further away from CSCs than high SES areas. As such, individuals from the poorest parts of Alberta may take longer to get to an EVT capable centre, thereby decreasing the odds they will be treated with EVT when suffering an ischemic stroke. Ultimately, these findings highlight the challenges of ensuring equitable distribution of time sensitive interventions to geographically isolated populations.

<u>SES and Access to EVT</u>

Prior to the advent of EVT, the best way of reperfusing ischemic brain during a stroke was IV thrombolysis with Alteplase.[3,31] This remained standard of care until the publication of several clinical trials in 2015 that showed EVT in addition to Alteplase was superior to Alteplase alone for treatment of ischemic stroke due to a large vessel occlusion in the anterior circulation.[4-8] Unfortunately, there are limited data on whether the benefits from this treatment advance has been equitably distributed along socioeconomic lines. Two American papers published in 2014 used data from the NIS database to assess the relationship between SES and EVT.[13,14] One looked at the years 2006-2010 and the other looked at only 2008. Both papers observed a statistically significant difference in the odds of being treated with EVT for patients living in areas with the lowest median income; however, both papers used data collected before EVT was considered standard of care. More recently, authors have again turned to the NIS database to address the relationship between SES and EVT with two more papers being published on the topic in 2021,[15,16] again finding that low SES individuals were less likely to be treated with EVT. Both papers used American data and did not restrict their cohorts to individuals who received

Alteplase for their ischemic stroke. While the paper by de Havenon and colleagues (2021) controlled for whether patients lived in an urban or rural area, neither study controlled for the distance an individual lives to the nearest CSC. To our knowledge, no study has investigated this question in Canada, which has a universal, publicly funded healthcare system, unlike the United States. This work included only individuals who were treated with Alteplase, which was the previous standard of care. Nonetheless, these results are notable for suggesting that disparities in access to acute stroke intervention between the most and least deprived individuals in Alberta is largely explained by the reality that deprived individuals tend to live further from CSCs than their more privileged peers.

Distance to a CSC, Neighborhood SES, and Access to EVT

The results of our mediation analysis suggest that the discrepancy in access to EVT based on neighborhood SES is mediated by the distance an individual lives to the nearest CSC. Although provinces in Canada are responsible for providing universal and accessible healthcare to all residents, the reality is more complicated. A recent review of Canada's health system argued that despite our universal healthcare, those living in rural and remote communities have less access to physical and human healthcare resources.[32] This is of particular relevance for time-sensitive interventions, such as EVT for ischemic stroke. Again, studies out of the United States suggest that individuals who live in rural areas are less likely to be brought to an EVT capable centre when suffering an ischemic stroke, and this significantly decreases the odds that they will receive treatment with EVT regardless of the facility's transfer capability.[33] That individuals who live far from CSCs are also less likely to receive EVT in Canada is unsurprising, as it is a time sensitive intervention.[11,12] Our results showed that individuals from the most deprived neighborhoods were significantly more likely to live further from CSCs than their peers from high SES areas. As such, it is likely that the relationship between access to EVT and living in low SES areas is mediated by the distance these individuals live from centres capable of performing this procedure. This problem is not easy to reconcile for Canadian policymakers, who are tasked with providing quality healthcare to a geographically dispersed population. However, it does suggest that improving access to EVT for individuals in more remote locations will have an additional benefit of ensuring more equitable access to this therapy for those living in low SES areas. Thankfully, recent trials have sought to expand the treatment window for EVT based on certain imaging characteristics,[9,10] which may improve equity in access to this revolutionary treatment.

Limitations and Future Directions

We acknowledge there are some limitations of this investigation. First, our cohort was restricted to individuals who received Alteplase as treatment for their ischemic stroke, which excludes any individual who presented outside the window for thrombolysis. This may systematically exclude low SES individuals if they are more likely to present to medical attention outside the treatment window for Alteplase. However, this did allow us to compare for whether any pre-existing disparities in access to acute stroke care were widened by the advent of EVT. Second, our independent variable of interest was neighborhood level SES, which may not be reflective of an individual's SES. Although neighborhood SES is associated with health outcomes, it does raise the possibility of the ecological fallacy.[34,35] Nonetheless, we felt that neighborhood SES was an appropriate independent variable given the limitations of administrative data. Lastly, our dataset did not contain a race variable, which may play a confounding role in the relationship between neighborhood SES and treatment decisions. However, previous works using the Pampalon index have found it to be predictive of adverse health outcomes even after accounting for race.[36] Future works should attempt to replicate these findings but not limit the study cohort to individuals treated with Alteplase. Furthermore, researchers should investigate whether individuals from low SES areas suffer worse outcomes and have longer times to treatment than their high SES peers. Lastly, these results do not assess the cost effectiveness of changes that might result in a more equitable distribution of EVT based on neighborhood level deprivation and the distance individuals live from a CSC. As such, future researchers may wish to perform a distributional cost-effectiveness analysis that accounts for improved equity and the finite resources of Alberta's health care system.

Conclusions

Our main analysis found a significant difference in the odds of receiving EVT after IV Alteplase for an ischemic stroke based on neighborhood SES. Further analysis showed that individuals in the lowest SES neighborhoods tend to live further from CSCs than individuals from high SES neighborhoods. Our results suggest that a key avenue for improving the equitable distribution of EVT is to improve access for individuals who live outside large urban centres.

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Figure Legends:

Figure 1: Combination of material and social deprivation quintiles to create a 5-group ordinal variable. Reproduced with permission.[26]

Figure 2: Relationship between deprivation levels and log transformed distances to the nearest CSC (Note: Distance log transformed for graphical purposes to better visualize differences)

Figure 3: Bar chart demonstrating the proportion of patients who had EVT attempted by deprivation level

Figure 4: Logistic regression lines of best fit demonstrating the predicted proportion of patients that will receive EVT based on the distance they live from the nearest CSC, stratified by their deprivation level. (Note: Figure 4 demonstrates that, for all deprivation levels, the expected proportion of patients that will be treated with EVT decreases as the distance to the nearest CSC increases.)

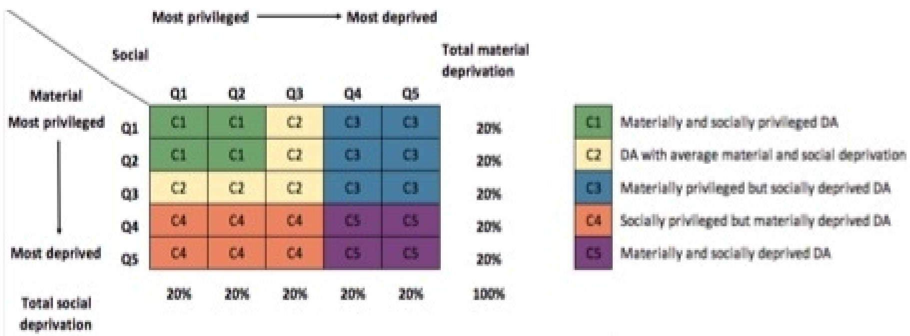

Figure 1: Combination of material and social deprivation quintiles to create a 5-group ordinal variable. Reproduced with permission.[26]

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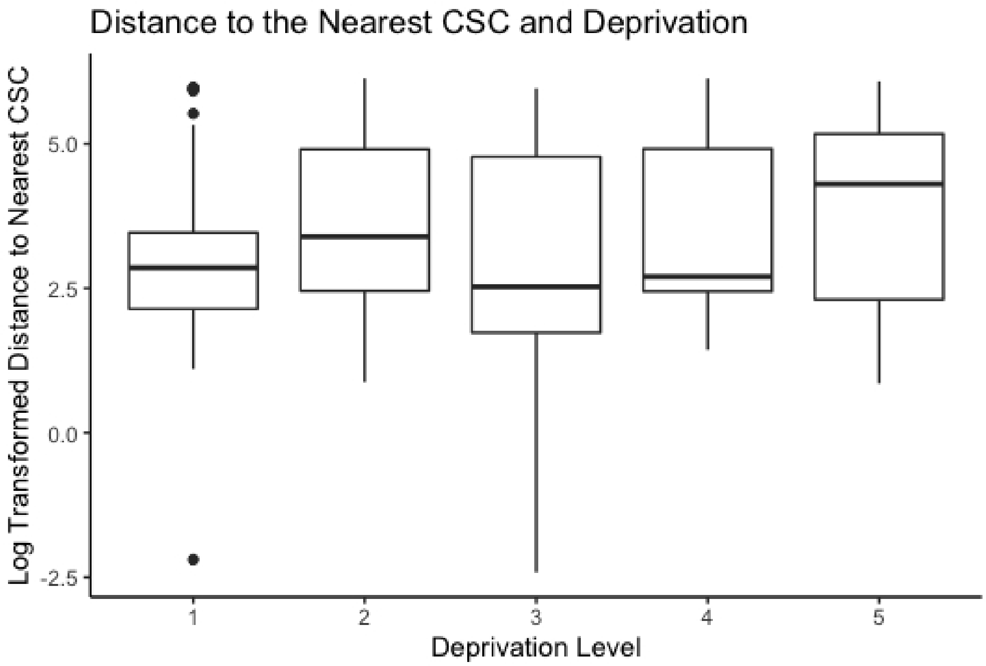
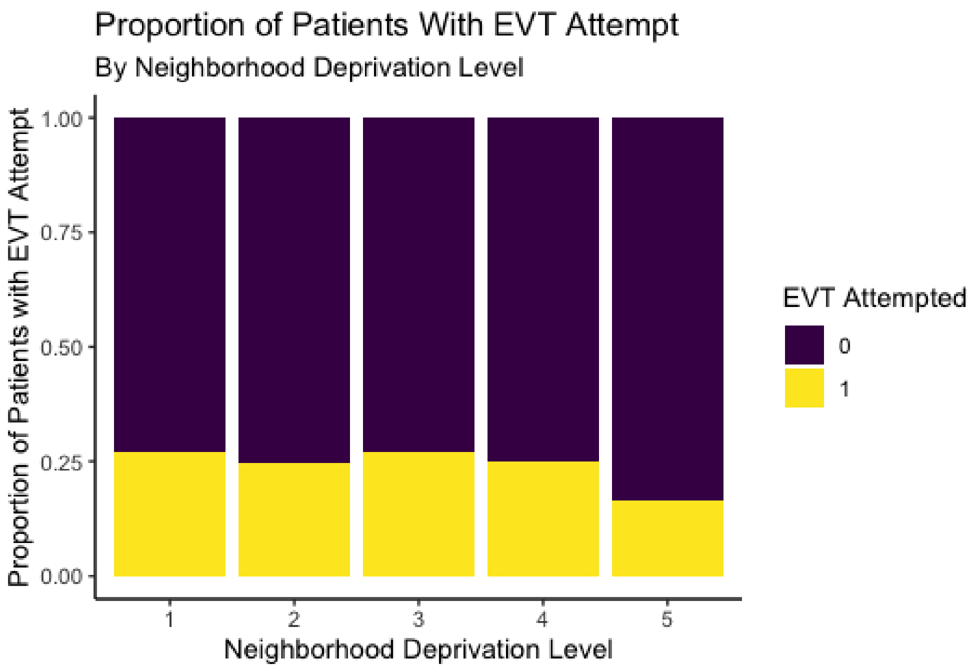


Figure 2: Relationship between deprivation levels and log transformed distances to the nearest CSC (Note: Distance log transformed for graphical purposes to better visualize differences)

189x128mm (72 x 72 DPI)



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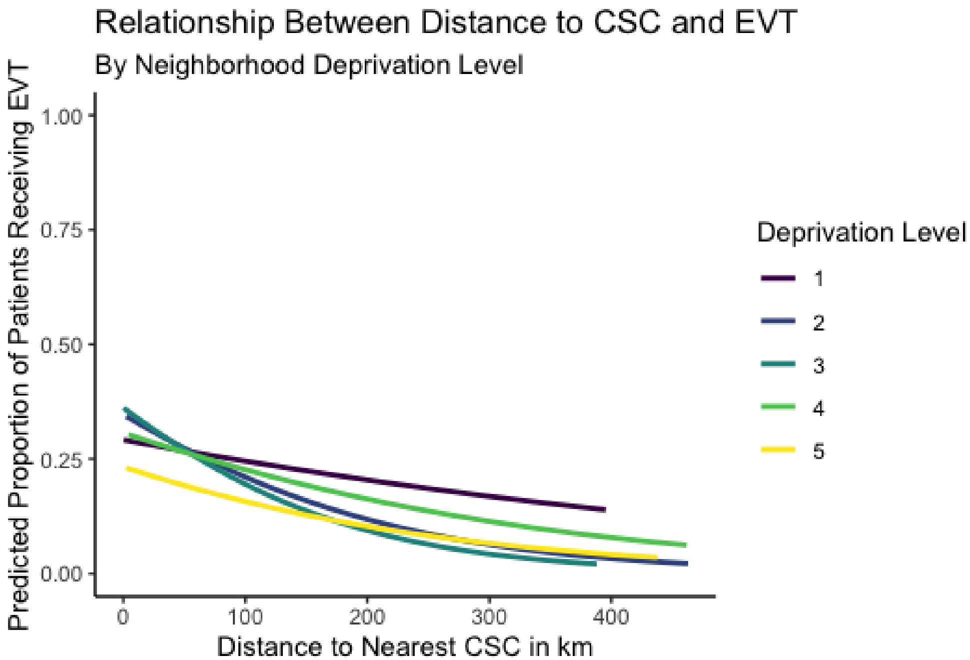

Figure 4: Logistic regression lines of best fit demonstrating the predicted proportion of patients that will receive EVT based on the distance they live from the nearest CSC, stratified by their deprivation level. (Note: Figure 4 demonstrates that, for all deprivation levels, the expected proportion of patients that will be treated with EVT decreases as the distance to the nearest CSC increases.)

189x128mm (72 x 72 DPI)

Table 1: Baseline and Clinical Characteristics of the Study Cohort

	Total (n = 1335)	EVT[b] Attempted (n = 314)	No EVT[b] Attempted (n = 1021)	*p*-value
Age (median, IQR[c])	72 (21)	71 (18)	73 (22)	< 0.001
Male Sex	731 (54.8%)	175 (55.7%)	556 (54.4%)	0.740
Pre-Alteplase NIHSS Grade (median, IQR[c])	9 (11)	17.5 (8)	8 (7)	< 0.001
Distance to Nearest CSC[a] in km (median, IQR[c])	22.5 (128)	13.6 (43.5)	29.8 (163)	< 0.001
Deprivation Grouping*[+]	1 - 157 (11.8%) 2- 251 (18.8%) 3 - 308 (23.1%) 4- 220 (16.5%) 5- 247 (18.5%)	1 – 42 (13.4%) 2 – 62 (19.7%) 3 – 81 (25.8%) 4 - 55 (17.5%) 5 - 40 (12.7%)	1 - 115 (11.3%) 2 – 189 (18.5%) 3 – 227 (22.2%) 4 – 165 (16.2%) 5 – 207 (20.3%)	0.040

* Missing 152 patients

[+] Level 1 is least deprived grouping

[a] Comprehensive Stroke Centre

[b] Endovascular Thrombectomy

[c] Interquartile Range

Table 2: Unadjusted Odds Ratios (95% CI, *p*-value) Deprivation Levels and EVT using complete data

Deprivation Level	OR*[b] (95% CI[a])	*p*-value
1	Reference Level	N/A
2	0.89 (0.56 – 1.41)	0.618
3	1.00 (0.65 – 1.56)	0.986
4	0.90 (0.56 – 1.43)	0.677
5	0.53 (0.32 – 0.87)	**0.011**

* Odds Ratios calculated in comparison to the least deprived deprivation level

[a] Confidence Interval

[b] Odds Ratio

Table 3: Adjusted Odds Ratios (95% CI, *p*-value) Deprivation Levels and EVT without distance as a covariate using complete data

Variable	OR*[c] (95% CI[a])	*p*-value
Deprivation Level 1	Reference Level	N/A
Deprivation Level 2	0.889 (0.521 – 1.527)	0.669
Deprivation Level 3	0.963 (0.577 – 1.622)	0.885
Deprivation Level 4	0.749 (0.428 – 1.315)	0.313
Deprivation Level 5	0.431 (0.240 – 0.769)	**0.005**
Age	0.981 (0.970 – 0.992)	**< 0.001**
Male Sex	1.030 (0.746 – 1.425)	0.856
Pre-Alteplase NIHSS Grade	1.201 (1.173 – 1.232)	**< 0.001**

* Odds Ratios calculated in comparison to the least deprived deprivation level

[a] Confidence Interval

[b] Comprehensive Stroke Centre

[c] National Institute of Health Stroke Scale

[d] Odds Ratio

Table 4: Adjusted Odds Ratios (95% CI, *p*-value) Deprivation Levels and EVT using complete data

Variable	OR*[c] (95% CI[a])	*p*-value
Deprivation Level 1	Reference Level	N/A
Deprivation Level 2	1.072 (0.615 – 1.880)	0.809
Deprivation Level 3	1.015 (0.597 – 1.742)	0.957
Deprivation Level 4	0.861 (0.482 – 1.543)	0.614
Deprivation Level 5	0.604 (0.330 – 1.103)	0.101
Age	0.976 (0.965 – 0.988)	**< 0.001**
Male Sex	0.989 (0.707 – 1.385)	0.948
Pre-Alteplase NIHSS Grade	1.219 (1.188 – 1.252)	**<0.001**
Distance to Nearest CSC[b] in km	0.992 (0.990 – 0.994)	**<0.001**

* Odds Ratios calculated in comparison to the least deprived deprivation level

[a] Confidence Interval

[b] Comprehensive Stroke Centre

[c] National Institute of Health Stroke Scale

[d] Odds Ratio