



Access to Endovascular Thrombectomy for Stroke in Rural Versus Urban Regions

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ABSTRACT: *Purpose:* Endovascular thrombectomy (EVT) significantly improves outcomes for acute ischemic stroke patients with large vessel occlusion (LVO) who present in a time sensitive manner. Prolonged EVT access times may reduce benefits for eligible patients. We evaluated the efficiency of EVT services including EVT rates, onset-to-CTA time and onset-to-groin puncture time in our province. *Materials and methods:* Three areas were defined: zone I- urban region, zone II-areas within 1 h drive distance from the Comprehensive Stroke Center (CSC); and zone III-areas more than 1hr drive distance from the CSC. In this retrospective cohort study, EVT rate, onset-to-groin puncture time and onset-to-CTA time were compared among the three groups using *Kruskal–Wallis* and *Wilcoxon* tests. *Results:* The EVT rate per 100,000 inhabitants for urban zone I was 8.6 as compared to 5.1 in zone II, and 7.5 in zone III. Compared to zone I (114 min; 95% CI (96, 132); n = 128), mean onset-to-CTA time was 19 min longer in zone II (133 min; 95% CI (77, 189); n = 23; p = 0.0459) and 103 min longer in zone III (217 min, 95% CI (162, 272); n = 44; p < 0.0001). Compared to zone I (209 min, 95% CI (181, 238)), mean onset-to-groin puncture time was 22 min longer in zone II (231 min, 95% CI (174, 288); p = 0.046) but 163 min longer in zone III (372 min, 95% CI (312, 432); p < 0.0001). *Conclusion:* EVT access in rural areas is considerably reduced with significantly longer onset-to-groin puncture times and onset-to-CTA times when compared to our urban area. This may help in modifying the patient transfer policy for EVT referral.

RÉSUMÉ : **Accès à la thrombectomie endovasculaire dans les cas d'accident vasculaire cérébral – Comparaison entre les milieux urbain et rural.** *Objectif :* La thrombectomie endovasculaire (TEV) améliore sensiblement les résultats cliniques chez les patients qui ont subi un accident vasculaire cérébral (AVC) ischémique des gros vaisseaux et qui consultent en temps opportun. Toutefois, une attente prolongée peut atténuer les bienfaits de l'intervention chez les patients admissibles. L'étude visait donc à évaluer l'efficacité des services de TEV au Manitoba, notamment les taux de TEV, le temps écoulé entre l'apparition des symptômes et l'angiographie par tomographie assistée par ordinateur (angio-TDM), et le temps écoulé entre l'apparition des symptômes et le moment de la ponction dans l'aîne. *Matériel et méthode :* Le territoire a été divisé en trois zones : I – milieu urbain; II – milieu rural, à une distance de plus de 1 heure de conduite du centre de traitement. Dans cette étude de cohortes rétrospective, le taux de TEV, le temps écoulé entre les symptômes et l'angio-TDM et celui écoulé entre les symptômes et la ponction dans l'aîne ont été comparés dans les trois groupes à l'aide des tests de Kruskal-Wallis et de Wilcoxon. *Résultats :* Le taux de TEV pour 100 000 habitants en zone I était de 8,6 contre 5,1 en zone II et 7,5 en zone III. Quant au délai moyen entre les symptômes et l'angio-TDM, il était 19 minutes plus long en zone II (133 min; IC à 95 % : 77–189; n = 23; p = 0,0459) et 103 minutes plus long en zone III (217 min; IC à 95 % : 162–272; n = 44; p < 0,0001) que celui en zone I (114 min; IC à 95 % : 96–132; n = 128). Pour ce qui est du délai moyen entre les symptômes et la ponction dans l'aîne, il était plus long de 22 minutes en zone II (231 min; IC à 95 % : 174–288; p = 0,046) et de 163 minutes en zone III (372 min; IC à 95 % : 312–432; p < 0,0001) que celui en zone I (209 min; IC à 95 % [181–238]). *Conclusion :* L'accès à la TEV est beaucoup plus long en milieu rural qu'en milieu urbain, notamment en ce qui concerne le temps écoulé entre les symptômes et la ponction dans l'aîne et celui écoulé entre les symptômes et l'angio-TDM. Aussi les résultats pourraient-ils donner lieu à une modification de la politique de mutation des patients en vue d'une TEV.

Keywords: Ischemic stroke, EVT, Rural, Onset-to-CTA time and onset-to-groin puncture time

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INTRODUCTION

Endovascular therapy (EVT) has become the standard of care in Canada for acute ischemic stroke with large vessel occlusion (LVO), presenting in the first 6 h from symptom onset.¹ However, this time window is being shifted to a tissue-based window due to the use of perfusion or collateral imaging.² Advanced

imaging has enabled us to treat patients up to 24 h since the promising results of the DAWN and DEFFUSE 3 Trials.^{3,4}

Despite an increase in the number of hospitals providing EVT in recent years, the prolonged times to access EVT may reduce benefits for eligible patients from remote areas.⁵ Canada is substantially rural and most rural hospitals lack appropriate

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resources to immediately treat patients with stroke.⁶ Furthermore, Manitoba's geography is mostly rural with almost half of the population living outside of the urban center; thus making rapid access for EVT a challenge.⁷

Previous studies suggest disparities regarding the use of intravenous (IV) recombinant tissue-type plasminogen activator (r-tPA) in urban-rural stroke care; reporting significant differences, with frequency of use of IV r-tPA in urban hospitals being four times that of rural hospitals.⁷ Adding to the urban/rural disparity is the fact that 89% of rural hospitals lack an in-hospital CT scanner which hinders the timely diagnosis of large vessel occlusion (LVO).⁸ However, in Manitoba it remains unclear whether rural patients have delayed or similar access to EVT services as compared to those patients living in an urban area close to a comprehensive stroke center (CSC). The purpose of this study was to investigate the efficiency of EVT services including EVT rate, onset-to-CTA time and onset-to-groin puncture time in our province.

MATERIALS AND METHODS

Study Setting

Our province has a total population of 1,278,365 with an area of 647,797 km².⁹ The Provincial Stroke Strategy plan was established in 2011. A stroke code system was designed to cover the entire province offering acute stroke care. The Health Sciences Centre (HSC), which is in Winnipeg, is the CSC. Important to note is the fact that the CSC is the only center in our province that offers CT perfusion. As of January 2019, seven TeleStroke Sites, which function as primary stroke centers (PSC) became operational. The Winnipeg metropolitan area also has one PSC, Saint Boniface Hospital, see Figure 1A.

Patients with suspected acute stroke are identified by Emergency Medical Services (EMS) personnel. The EMS stroke protocol includes the use of the Cincinnati Prehospital Stroke scale and the Los Angeles Motor Stroke Scale (LAMS). Additionally, EMS personnel follow "contraindication to IV r-tPA" criteria, which may warrant a direct transfer to the CSC. A proximity map is then used to transfer potential stroke patients to the nearest stroke center or direct to the CSC if indicated. At the PSC, the patient is assessed by a neurologist (either in person or by TeleStroke) and undergoes a plain CT of head and a CT angiogram (CTA) of head and neck. Based on the patients' symptoms and their imaging findings, eligible patients receive IV r-tPA. Based on the results of the consultation with the neurologist and the interventional neuroradiologist, patients with LVO on the scan may be transferred to the CSC for EVT.

The EVT Selection Criteria in 2018 and 2019

The EVT selection criteria¹⁰ in 2018 included: patients older than 18 years of age (no upper age limit); symptoms of acute ischemic stroke with a score of 5 or higher on the National Institutes of Health Stroke Scale (NIHSS); an occlusion of the distal intracranial carotid artery, middle cerebral artery (M1 or M2), basilar artery and posterior cerebral artery (P1) on CTA; and that EVT could be initiated within 6 h from stroke onset.

In early 2019, with the publication of DAWN and DEFFUSE3 clinical trials, the selection criteria was expanded to include

patients with acute ischemic stroke up to 24 h from stroke symptom onset. These patients are selected based on their CT perfusion scans obtained at the CSC to confirm favorable maps with a small infarct core.

Based on this evidence, in Manitoba (since late 2018) all patients with signs of a disabling stroke that present to a stroke center within 6 h of symptom onset are assessed for LVO and potential treatment with EVT. If patients present between 6 and 24 h of symptom onset a case-by-case consultation with the HSC Neurologist on-call is undertaken.

Patient Characteristics

The study was approved from our institutional research ethics board. Patients were identified from our site's interventional neuroradiology registry, which lists all patients who undergo EVT. The data was then retrospectively collected on patients who underwent EVT between January 1st, 2018 and December 31st, 2019. Demographic information, stroke severity on NIHSS at CSC admission, stroke process parameters (onset-to-CTA time interval and onset-to-groin puncture time interval); rt-PA treatment status and thrombolysis in cerebral infarct (TICI) score were assessed. The province of Manitoba was divided into 3 zones based on distance from the CSC in the capital region. The distance was calculated from the patients' postal code address. Zone I included the metropolitan area of Winnipeg less than 15 km to the CSC with a population of 0.73 million. Zone II included the rural area located less than 1 h drive distance (i.e., a distance of between 15 and 50 km) from CSC with a population of 0.23 million. Zone III included the rural area which is more than 1 h drive distance (i.e., more than 50 km distance); from the CSC with a population of approximately 0.29 million (Figure 1A). Of note, Zone III is a large area with a minimum travel distance of 61.8 km, a median distance of 156.6 km and maximum distance of 924.7 km. Zone I is covered directly by the CSC, whereas zone II and III are primarily covered by PSCs under the provincial stroke strategy plan.

Statistical Analysis

Baseline characteristics were compared using independent sample t-test for normally distributed continuous variables, Kruskal–Wallis and Wilcoxon tests were used for non-normally distributed continuous variables, and the χ^2 test was used for categorical variables. The first outcome variable was the population rate of EVT (defined as the number of EVT treatments per ~100,000 population/year). Onset-to-CTA, which is the time interval in minutes between stroke symptom onset and the start time of the CTA and onset-to-groin puncture, which is the time interval in minutes between stroke symptom onset and groin puncture were compared among the three zones using Kruskal–Wallis (three groups) and Wilcoxon tests (two groups). If a patient had several CTAs, the onset-to-CTA time interval was calculated by using the first CTA, which could occur either at the PSC or CSC. The association between distance from the CSC and time of onset-to-groin puncture was analyzed using general linear regression model. All analyses were performed using SAS 9.4 (SAS Inc., Cary, NC, USA). The level of statistical significance for all analyses was set at α 0.05.

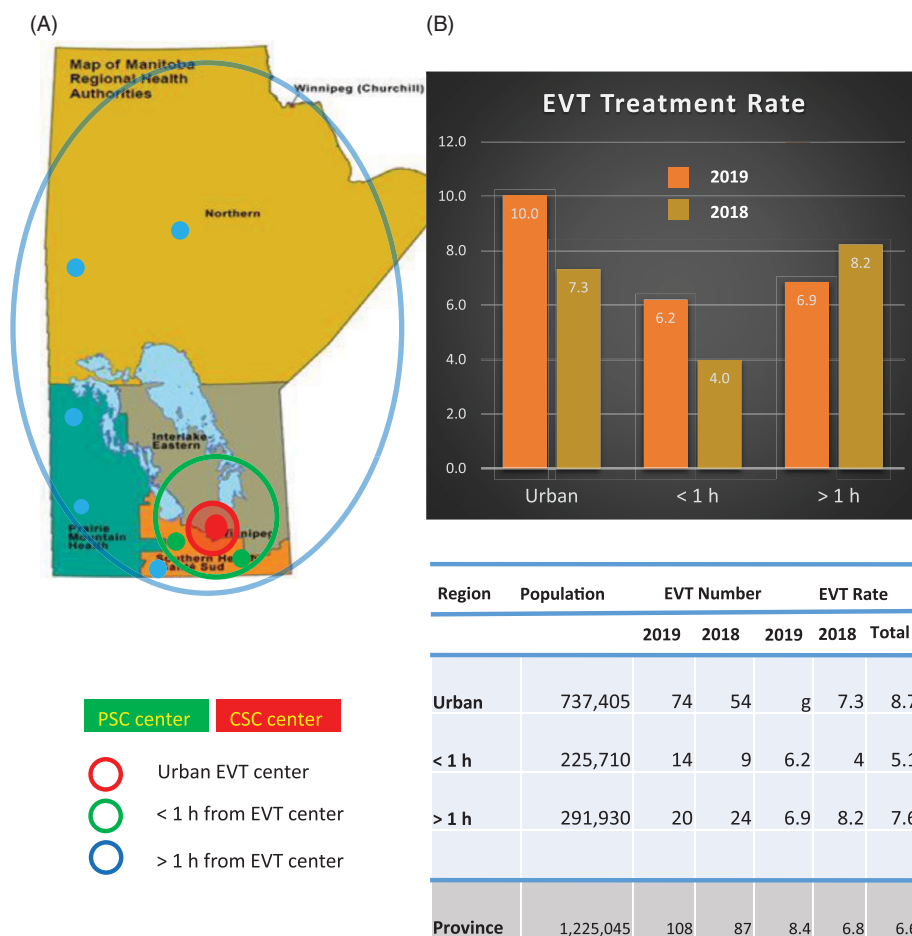


Figure 1: (A) Our province was divided into three areas based on the distance (calculated by postal code) to the CSC in the capital city. Zone I corresponds to the metropolitan area < 15 km to CSC, Health Science Center. Zone II includes areas primarily covered by CSC but located < 1 h away from a CSC (maximum distance 50 km). Finally, Zone III includes the areas primarily covered by local stroke centers (PSC) and > 1 h from the CSC (more than 50 km distance). PSCs include 8 hospitals which provide acute stroke services 24/7 in our province. The CSC is the EVT center in the capital city. (B) Population endovascular treatment rates (per 100,000 inhabitants) by urban region zone I (Winnipeg) or rural region including Zone II and Zone III (outside of urban region). The EVT rates in 2018 and 2019 were calculated. The average EVT rate was also shown.

RESULTS

A total of 204 patients were treated with EVT at the CSC during the 2-year study period. Nine patients without clear time of stroke onset including six “wake-up” stroke patients were excluded from the analysis.

EVT Rate

Of the 195 study patients, 128 (65.6%) lived in zone I, 23 (11.8%) lived in zone II, and 44 (22.6%) lived in zone III. There were no significant differences between the three zones in terms of age, sex, stroke severity, and rates of rt-PA treatment (Table 1).

As expected, the EVT rate was highest in urban Zone I (8.7 per 100,000 population). The Zone II EVT rate was 5.1 per 100,000 inhabitants and the Zone III EVT rate was 7.6 per 100,000 inhabitants (Figure 1). The EVT rate in zone I increased in 2019 compared to 2018 (8.4 per 100,000 inhabitants in 2019 compared to 6.6 per 100,000 inhabitants in 2018, $p = 0.07$). The

average EVT rate in the other two zones remained similar between the 2 years of study period.

Treatment Time

The mean onset-to-CTA time in zone I (114 min; 95% CI (96, 132); $n = 128$) was 19 min shorter compared to zone II (133 min; 95% CI (77, 189); $n = 23$; $p = 0.0459$), and 103 min shorter compared to zone III (217 min, 95% CI (162, 272); $n = 44$; $p < 0.0001$).

The mean onset-to-groin puncture time in zone I (209 min, 95% CI (181, 238); $n = 128$) was 22 min shorter compared to zone II (231 min, 95% CI (174, 288); $p = 0.046$; $n = 23$) and 163 min shorter compared to zone III (372 min, 95% CI (312, 432); $p < 0.0001$; $n = 44$) (Figure 2A). The trend of a longer mean onset-to-groin puncture time and onset-to-CTA time in zone III patients who lived further away from CSC was similar in both 2018 and 2019. The mean onset-to-groin puncture time had a positive association with the distance between onset and CSC on

Table 1: Baseline characteristics

	Urban (n = 128)	<1 h (n = 23)	>1 h (n = 44)	p-value
Age	76 (95% CI 70, 75)	71 (95% CI 64, 76)	74 (95% CI 68, 77)	0.62
Gender (Male (%))	46	48	52	0.46
NIHSS	14 (95% CI 12.7, 15.7)	15 (95% CI 11.2, 18.5)	13 (95% CI 10.4, 16.1)	0.76
tPA	55%	47%	50%	0.28
TICI (3 and 2b (%))	77%	85%	70%	0.2
Occlusion site				
Left (M1 and M2)%	50%	55%	53%	0.98
Right (M1 and M2)%	39%	35%	35%	
Basilar (%)	11%	10%	12%	

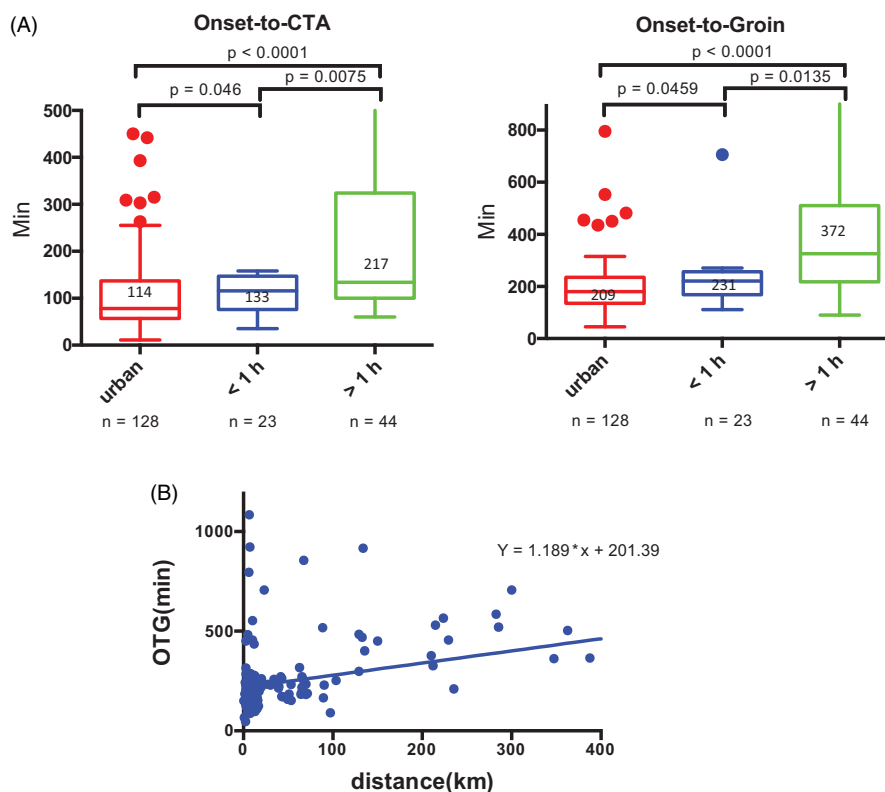


Figure 2: (A) Difference between onset-to-CTA time and onset-to-groin puncture time among Zone I, II and III areas described in Figure 1. The total number of two years were combined and compared among above groups using Wilcoxon or Kruskal–Wallis tests. The p-value was highlighted. (B) The association between two variables distance and onset-to-groin time was analyzed using simple liner regression model.

linear regression model ($k = 0.189$, $b = 201.39$; $R^2 = 0.265$; $p < 0.001$) (Figure 2B).

DISCUSSION

Our center demonstrated an increase in the number of EVT cases done in 2019 as compared to 2018. However, these remain lower than the national benchmark. The prevalence of LVO in people with acute ischemic strokes ranges from 13% to 42.6%.^{11–13} It has been reported that approximately 11.1% of patients with acute ischemic stroke receive EVT as treatment.¹⁴ Approximately 2000 patients

with a primary diagnosis of stroke are admitted to Manitoba hospitals annually according to the Discharge Abstract Database (DAD) in Manitoba. Based on this statistic and the EVT treatment recommendations, one can conservatively estimate that approximately 200 stroke patients in Manitoba should receive EVT annually.

Urban dwellers, which live in zone I, comprise 70% of Manitoba's population. Based on global EVT benchmarks, a conservative estimate would be to expect 140 patients with stroke to undergo EVT in zone I annually. However, we found that not

even urban dwellers in zone I met the national standard for EVT treatment. Although not significant, our study did find that there was an increase in EVT procedures per 100,000 inhabitants in 2019 as compared to 2018. This is promising and highlights the need for ongoing data collection and quality improvement. However, of great concern are the disparities that do exist between urban and rural areas regarding access to EVT for stroke in our province.

To the best of our knowledge, this is the first study to describe variation of EVT rates and efficiency in Canadian rural and urban regions. We observed that accessibility to EVT in these rural areas was lower with significantly longer onset-to-groin puncture times and onset-to-CTA times when compared to urban areas (Figure 2). Of importance is the fact that Zone III, which includes regions >1 h drive distance from the CSC has a large region with a minimum distance of 61.8 km, a median distance of 156.6 km, and a maximum distance 924.7 km. Canada's vast geography creates challenges for prompt transport to hospital. It has been previously shown that it takes about 4–7 h to transfer a patient to a CSC from a remote area for EVT, and even longer in winter conditions considering climatic and geographic barriers.⁵ Our data is consistent with this, as reflected by the mean onset-to-groin puncture time of approximately 372 min from remote areas. To transfer from a PSC to a CSC for EVT is time-consuming, likely reducing the effectiveness of EVT.^{2,15} The delay in the early diagnosis through CT angiogram in rural zones was reflected in the longer onset-to-CTA time in these regions. Additional interventional neuroradiology services in rural regions are neither feasible nor cost-effective in the Canadian and specifically the Manitoba landscape. However, making CTA available at every PSC during all hours of the day and week could potentially optimize the onset-to-CTA time and also better onset-to-groin puncture time. In order to improve the onset-to-groin puncture time some suggest the use of a robotic EVT.¹⁶ The pre-thrombectomy cytoprotection such as NA-1 could be used for the remote onset of LVO.¹⁷ Even though robotic EVT and cytoprotection may not be currently feasible, it is important to improve access to care for patients with LVO strokes in rural Manitoba. This is the first process metric data describing EVT processes of care for patients receiving EVT in our province. Importantly, our study findings serve as a baseline from which processes in EVT stroke care can be improved upon.

Most jurisdictions use a pre-hospital acute stroke triage system where paramedics transport a patient with suspected acute ischemic stroke to the nearest PSC for a diagnostic work-up and to initiate IV rt-PA if eligible. Patients who are eligible for EVT are then transferred to a CSC. Studies show that this “drip-and-ship” system delays initiation of EVT by 40–106 min and decreases the chance of a good clinical outcome by approximately 10%.^{18–22} Despite this clear disadvantage, the “drip-and-ship” system is currently the most feasible model when considering the acute emergency services setting. Directly presenting all patients with suspected LVO to a CSC would overburden these hospitals.²³ Therefore, a reliable pre-hospital triage method is the key to ensure that patients with a LVO are rapidly identified and promptly transferred to CSC.

Rapid Arterial Occlusion Evaluation Scale (RACE) and The National Institute of Health Stroke Scale (NIHSS) are the commonly used non-image diagnostic methods for triaging LVO.

However, their false negative rates remain higher and thus, at least 20% patients with LVO are incorrectly transferred to a PSC with no EVT service.^{24,25} In Manitoba, the LAMS stroke severity triage tool was adopted. Theoretically, for patients with a contraindication for IV rt-PA, no valuable time would be lost by bypassing the PSC and going directly to a CSC if the CSC is within a certain distance.²² Our province has adopted this system where a patient with a contradiction to rt-PA will be re-routed directly to the CSC, if the CSC is within a certain distance. In the regional scenario where a short transportation time to a CSC could be achieved, a direct transfer to the CSC might be the preferable approach even if that means that bypassing the PSC would result in a longer transportation time.¹⁷ In cases of high probability of LVO, even longer transportation delays maybe justifiable.²³ However, patients with ischemic stroke receiving EVT care exclusively in CSC were not necessarily associated with better overall outcomes.²⁴ A preliminary analysis of our own outcomes suggested suboptimal outcomes from EVT in our center.¹⁵ Further analysis for the underlying causes for the suboptimal outcomes is ongoing.

Our study is limited in its retrospective nature. The underlying reasons for differences in “EVT rate” were not illustrated. In order to fully understand this difference, we will need to calculate for the cases with acute ischemic stroke, the proportion of patients who underwent CTAs, the rate of positive LVO, and proportion of patients with LVO who are treated in all three zones.¹³

In addition, we did not take the final outcome for all of our patients. Further study is required to evaluate whether a pre-hospital triage system to determine either a nearest PSC or bypass the closest PSC to bring the patient to CSC offering EVT changed the long-term functional outcomes in our patients. For this study, we primarily focused on the stroke process and access to EVT in our province.

CONCLUSION

Accessibility to EVT from outside the urban area is significantly reduced with significantly longer onset-to-groin puncture times and onset-to-CTA times when compared to urban area. This may help in modifying the patient transfer policy for EVT referral.

CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

STATEMENT OF AUTHORSHIP

YY, KH and JS were involved in the conception and design, literature search, data acquisition, data analysis, drafting of the initial manuscript, and critical revision for important intellectual content. SA, EG, AT and JM were involved in data acquisition, data analysis, and editing the manuscript. All authors read and approved the final manuscript.

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