# Functional Outcomes and Mortality Rates for Ischemic Stroke Patients Presenting to Rural Hospitals or Urban Hospitals in Pennsylvania

by

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## Abstract

Stroke is the fifth leading cause of death in the United States and is a major public health concern worldwide. Most strokes are caused when clots form in a vessel and block blood flow. Tissue plasminogen activator (tPA) can be used to dissolve the clot quickly. Most debilitating strokes are caused by large vessel occlusion (LVO). Patients in rural areas often lack timely access to specialty stroke care, thus transfer to tertiary hospitals may be necessary to access time-sensitive endovascular therapies (ET) needed for LVO. We hypothesized that stroke patients from rural areas in Pennsylvania would have decreased functional outcome and higher mortality rates compared to those from urban areas. Data were collected on patients in a large regional health system with confirmed ischemic stroke from January 2014 to December 2015. Rural hospitals were defined as those located in counties designated as rural by the Center for Rural Pennsylvania. Time to intervention, mortality, and functional outcome measured by the modified Rankin scale (mRS), were compared between rural and urban centers. Results of the study showed that stroke patients discharged from rural hospitals do not have more severe functional outcomes or higher mortality rates. Thus, there is no significant difference in outcome measures between rural and urban hospitals among an integrated health delivery system (UPMC) in Western Pennsylvania.

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# 1.0 Introduction

## 1.1 What Is Stroke?

Stroke is the fifth leading cause of death and leading cause of serious long-term disability in the United States.[1] A stroke occurs when blood vessels carrying oxygen and nutrients to the brain are blocked or reduced. The blockage deprives brain tissue of oxygen and nutrients which can lead to brain cell death. In the U.S., it is estimated that 87% of all strokes are ischemic strokes, which are caused by an abrupt blockage of blood vessels leading to the brain.[3] The blockages are most often (~87%) caused by clots which interrupt blood flow and deprive the brain of oxygen and lead to brain cell death if the clot is not dissolved or removed.[7] Hemorrhagic strokes, accounting for about 13% of stroke diagnoses, are caused by an artery rupturing and damaging brain cells.[7] A transient ischemic attack (TIA) or a "mini-stroke" is caused by a temporary clot in which stroke symptoms last for a short time (less than 24 hours) then resolves. Having a TIA increases the risk of having an ischemic stroke.[5]

Though there are various types of stroke, they all have similar presentations. Paying attention to when signs and symptoms begin and how long they last is important when seeking stroke treatment. The length of time from stroke symptom onset to clinical care is especially important since the time can affect treatment options. Every minute counts during a stroke. The longer an individual goes without treatment, the more brain damage there may be. According to the American Heart Association (AHA), someone in the U.S. has a stroke every 40 seconds on average.[2] Each year in the United States, about 795,000 people have a stroke.[2] Of these, about 600,000 are first attacks and 185,000 are recurrent attacks.[2] Disability following stroke is defined

by the modified Rankin Scale (mRS).[8] Patients are assigned into one of seven categories from no disability to death following a stroke, shown in Table 7.

To increase public awareness of stroke, the National Stroke Association and the American Heart Association created the acronym FAST (Facial drooping, Arm weakness, Speech difficulties, Time to call 9-11).[30] Other signs of a stroke may include, but are not limited to: sudden numbness or weakness in the face or an extremity (especially if it's on one side of the body), confusion, trouble speaking, difficulty understanding speech, trouble seeing in one or both eyes, trouble walking, dizziness, loss of balance, lack of coordination, or sudden severe headache with unknown cause.[30] If patients seek and receive appropriate care, it can help prevent long-lasting brain damage, long-term disability, or even death through early intervention.

## 1.2 Risk Factors for Stroke in the United States

It is vital to know the factors that contribute to stroke and stroke outcomes. The community individuals live in, the distance from the hospital, and the type of hospital that is the closest may also affect stroke patients' outcomes. If an individual has a stroke and lives in a small, remote rural community that is noticeably far away from the nearest hospital, there is a chance that the individual will not have a good outcome. Living far away from a hospital or not being able to recognize stroke symptom may lead to delayed time to intervention, which could impact patient outcome. Most strokes (80%) are preventable through screening for and addressing known risk factors.[6]

Risk factors can be classified as modifiable and non-modifiable. Modifiable risk factors include factors such as hypertension, smoking, diabetes mellitus, atrial fibrillation, and obesity.[32]

These risk factors are highly preventable. Hypertension is one of the most important risk factors for stroke since people with hypertension are about 3 or 4 times more likely to have a stroke.[6] Hypertension can weaken and damage blood vessels that supply blood to the brain. Non-modifiable risk factors include age, race, and gender. Age is the strongest determinant of stroke. Only one-fourth of strokes occur in people under the age of 65, and each decade after the age of 55, the risk of stroke more than doubles.[6] Black patients with hypertension (41.2%) are two times more likely to have a stroke than whites (28%), meaning that hypertension is a potentially more potent risk factor among black patients when predicting stroke.[6] Further, gender can play a role in determining stroke. Even though men have a higher age-adjusted prevalence rate for stroke, women tend to live longer and thus have a higher lifetime risk for stroke than men.[2] Approximately 60% of the people who die from stroke are women, who also tend to have worse functional outcomes[6]. This means that after a stroke, it is more difficult for women to return to their baseline activities of daily living and quality of life. Other risk factors can include where people live, which may impact diet and access to healthcare, as well as social and economic factors.[32]

### 1.3 Stroke Care Interventions

Emergency treatment for stroke depends on the type of stroke, such as ischemic or hemorrhagic. Ischemic strokes, which are the most common, can be treated either by medications to dissolve the clot or endovascular procedures to remove the clot mechanically. Emergency treatments with medications include the use of clot-busting drugs, such as tissue plasminogen activator (tPA).[9] Giving an intravenous (IV) injection of tPA is the standard treatment for acute

ischemic strokes. This is where time of stroke symptom onset plays an important role since it is recommended that tPA be given within 3-4.5 hours from onset of stroke symptoms.[9]

Endovascular treatment (ET) often results in a higher rate of recanalization, or restoring blood flow, in ischemic stroke patients.[12] ET involves using a catheter to maneuver a stent retriever to remove the clot. This treatment is beneficial for people with large vessel occlusion (LVO) that cannot be treated or completely treated with tPA.[9,10] However, there is a narrow window in which reperfusion can be accomplished since the benefit of it decreases over time.[9] Since stroke is important public health issue, one of the ongoing strategies to improve stroke care has been to increase the accuracy and speed of acute stroke management. Khandelwal, et al. outlines (shown in Figure 1) an overall approach to implementing a new standard of care for patients with acute ischemic stroke who have LVO.

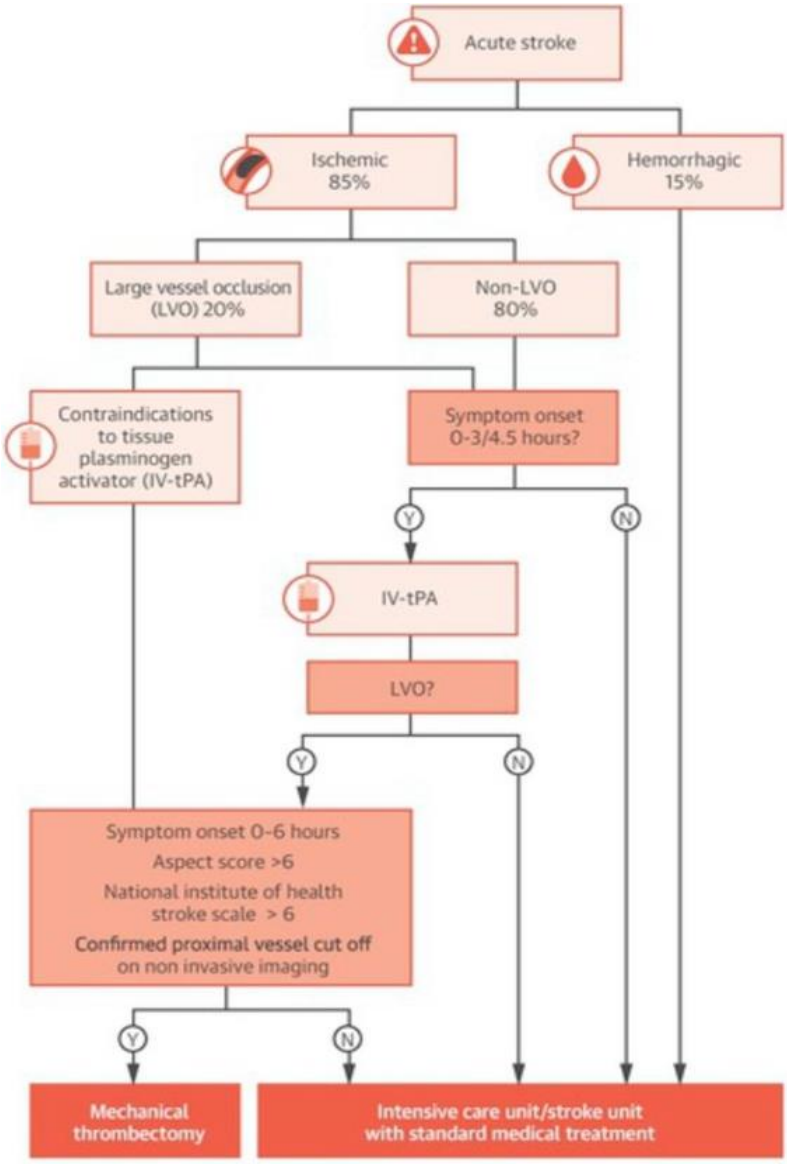


**Figure 1. New Standard-of-Care in Acute Ischemic Stroke Intervention: Mechanical Thrombectomy with IV-tPA for LVO Ischemic Stroke**

### 1.4 Types of Stroke Facilities

There are five types of facilities stroke patients can be taken to: non-stroke centers, acute stroke ready hospital (ASRH), primary stroke centers (PSC), thrombectomy-capable stroke

centers (TSC), and comprehensive stroke centers (CSC). Stroke patients that are far from a certified stroke facility are taken to the closest hospital, which is oftentimes a non-stroke center. When a patient is more than two hours from a PSC or CSC, they are then taken to the closest ASRH.[11] Many patients that have an acute stroke live in areas without access to a PSC or CSC. Studies have shown that at least 50% of the U.S. population live more than 60 minutes away from a PSC.[11, 13] ASRH were created for acute care since many stroke patients did not have ready access to a stroke center, but did have access to the local rural hospitals. ASRH are able to complete a CT scan to diagnose stroke, have access to stroke expertise (either onsite or through telemedicine), and administer tPA, if needed, prior to transferring patient to a PSC or CSC.[11]

PSCs are equipped to provide emergent care, such as giving tPA, and more extensive evaluation and care than an acute stroke ready center does to help stabilize a patient.[14] Some patients may need more advanced interventional procedures, though, which many PSCs do not offer. PSC takes care of most ischemic strokes, but does not have access to invasive catheter procedures, specialized intensive care unit for stroke patients, or access to neurosurgery within 2 hours: these centers send patients in need of these expertise to CSC.[14-16] Although there is an increasing number of PSCs, access to PSCs varies by region. PSCs give patients a chance at the best possible outcome in underserved regions if there is no CSC available within two hours of the patient's location.[16]

TSCs were created to provide an intermediate level of care between PSCs and CSCs. The TSC certification has raised concerns since it allows PSCs to provide thrombectomies without meeting all the requirements for a CSC.[8] For instance, a major concern with TSC is that physicians who perform the thrombectomies no longer require certification by the Society of Neurological Surgeons' Committee on Advanced Subspecialty Training (CAST).[8, 21] Studies

have shown that stroke patients that received thrombectomies at TSCs have fewer positive outcomes than those at CSCs.[10] TSCs focus specifically on performing endovascular therapies, but does not provide specialty care like CSCs.[9,11]

CSC care for all types of strokes, has 24/7 access to catheter based procedures to treat stroke, a dedicated neuroscience intensive care unit for stroke patients, 24/7 on site neurosurgical availability, and receives patients from PSCs.[24] If there is no CSC available within two hours of a stroke patient's location, the patient is then taken to a PSC.

### 1.5 Rural-Urban Differences in Acute Stroke Management Practices

Stroke mortality is 30% higher in rural compared to urban areas in the United States, and this seems to be due to higher incidence of stroke rather than stroke case fatality.[3,18] About 25% of the U.S. population lives in rural areas that are a considerable distance or are remote from large hospitals that can provide high level stroke care.[17] Living far away from a hospital that can provide the appropriate care, or being transported to a higher-level hospital may delay time-sensitive treatment such as tPA. The time to intervention is extremely important, especially if the stroke is severe. Rural stroke victims and their caregivers are less likely to recognize stroke symptoms, dispatchers and prehospital providers in rural areas are less likely to identify stroke, rural providers may have limited training in treating stroke patients, and patients in rural areas may experience longer transport times.[17] All these factors contribute to challenges rural areas may face compared to urban areas. Once arriving at a hospital, rural stroke patients may be less likely to receive interventions, such as tPA, since providers may have limited training. The

providers may also be less informed about advances in stroke management and disincentivized to transfer due to increased cost to the patient or reimbursement for the rural hospital.[17]

Rural stroke patients often differ from their urban counterparts by comorbidities, risk factor control, quality of stroke care, and less access to stroke specialists.[20] Rural residents are also at a higher risk for stroke for numerous reasons including a higher elderly population and a higher prevalence of diabetes mellitus, cardiovascular disease, and smoking.[17] Even though these residents are at a higher risk for stroke, rural hospitals lack stroke specialists which often leads to primary care physicians managing acute stroke care in these areas.

### 1.6 Stroke Related Health Care Cost in the U.S.

Stroke is a debilitating disease that has a major economic impact on survivors. The burden of stroke not only lies in the high mortality, but also the high morbidity that results in about 50% of survivors being chronically disabled.[18] Patients left with long-term disability after stroke may require special care or may live in skilled nursing facilities or other long-term healthcare facilities that contribute to the high cost of stroke. As the population grows and continues to get older, incidence of stroke has increased in younger generations as well despite major strides in stroke treatment.[22] The average lifetime cost per ischemic stroke patient in the U.S., which includes inpatient care, rehabilitation services, and follow-up care, is $140,048.[19] The American Heart Association estimates a total cost of stroke to increase from $105.2 billion in 2012 to $240.7 billion by 2030.[18] Higher incidence of stroke has led to increased financial burden on patients and their caregivers.

## 1.7 Gaps in Knowledge

Stroke incidence and mortality are higher in rural areas compared to urban areas in North America, but the reasons for this difference is not well understood.[18] Disparities between rural and urban population with respect to the outcomes of survival (mortality) and functional status as measured by the modified Rankin Scale (mRS) are not well described. Some causes may include differences in vascular risk factors, socioeconomic status, differential quality of care, and differential access to care.[21] We wanted to find whether there was a difference in functional outcome of the patient when presenting from a rural or urban area in Pennsylvania. Pennsylvania has 67 counties, with 48 being rural.[29] Western Pennsylvania only has 4 comprehensive stroke centers, 3 in Allegheny and 1 in Erie, all in urban counties.

Rural hospitals often have less access to specialty services, fewer options for interventions, and less funding to invest in advanced care than urban hospitals. When residents reach rural hospitals, these centers tend to have fewer health care professionals, including stroke specialists, that can treat complicated stroke cases.[27] Thus, rural hospitals may face equal or greater challenges when trying to deliver high quality stroke care to LVO patients.

Ischemic stroke patients with LVO need access to specialized care quickly. Though about 10% to 27% of stroke patients experience an LVO, only a small minority (< 5%) receive ET.[12] One of the most significant factors for undertreatment with ET is delayed presentation to hospitals in which these specialized procedures can be performed.[26] Since rural hospitals often lack the resources to care for LVO, these patients are diagnosed and transferred much later than they should be which can further put the patient at risk for a worse functional outcome.[35] Thus, transferring patients with LVO to hospitals without interventional treatment options for complicated strokes is an unresolved issue that is most pronounced in rural areas.[26, 27] Not only

does secondary transfer between hospitals delay care and increases the risk of worse functional outcome, but it also costs a considerable amount for patients.

### 1.8 Public Health Significance

According to the American Stroke Association (ASA), someone in the U.S. has a stroke every 40 seconds on average.[2] With an annual mortality rate of about 5.5 million, stroke has become the second leading cause of death worldwide.[18] Its high mortality and morbidity rates have caused stroke to become a public health burden, both globally and in the United States. This high burden could be due to lack of knowledge of risk factors and warning signs of stroke in communities. The number of survivors left with moderate or severe disabilities has also risen with increased incident of stroke.[18]

Many strokes can be prevented by screening for and addressing preventable risk factors. Public health measures that can be taken for stroke prevention may include surveillance to identify areas in which gaps in stroke care delivery exist, as well as monitoring and evaluating progress to reduce those gaps. Educating emergency physicians and staff in smaller hospitals on new acute stroke management may aid in improving and providing more access to stroke care in areas where it is difficult to receive higher care for complex strokes, such as for LVO patients.[28] Furthermore, programs can be implemented to educate people on how to reduce their risk of stroke. Since stroke is the leading cause of long-term disability reducing the incidence and complications of stroke, may reduce the number of people with moderate or severe disabilities.

## 2.0 Objective

The objective of this report is to compare the functional outcomes (mRS) and mortality rates of stroke patients presenting to rural versus urban hospitals in Pennsylvania between January 2014 and December 2015. Furthermore, time to intervention will be analyzed to determine if time had an impact on patient outcomes at discharge between rural and urban hospitals during the same time period. Results of these analyses may help to inform and influence health practice and health policy regarding intervention for acute ischemic stroke.

# 3.0 Methods

## 3.1 Selection of Participants

From January 2014 to December 2015, pre-hospital emergency medical services (EMS) records were selected for inclusion by a text word search in the chief complaint field for the word “stroke” or a coded entry for stroke-like symptoms. This study was approved by the University of Pittsburgh Human Subjects Research Protection Office. Since we only had access to University of Pittsburgh Medical Center (UPMC) patient medical records, the search was limited to patients that were taken to a UPMC facility. This included 16 UPMC hospitals, 7 rural and 9 urban, covering a population of roughly 4 million people in Western Pennsylvania. Figure 3 in shows the spatial distribution of the hospitals. We identified patients with a final diagnosis of ischemic stroke as classified by the International Statistical Classification of Diseases and Related Health Problems (ICD-9 and ICD-10). Final diagnoses were found in the patients’ medical records. Rural hospitals were defined as those located in counties with a rural designation by the Center for Rural Pennsylvania. Patients were excluded if the data were incomplete, EMS picked patients up from out of state, or if there were non-strokes. Figure 2 depicts inclusion and exclusion of the study population.

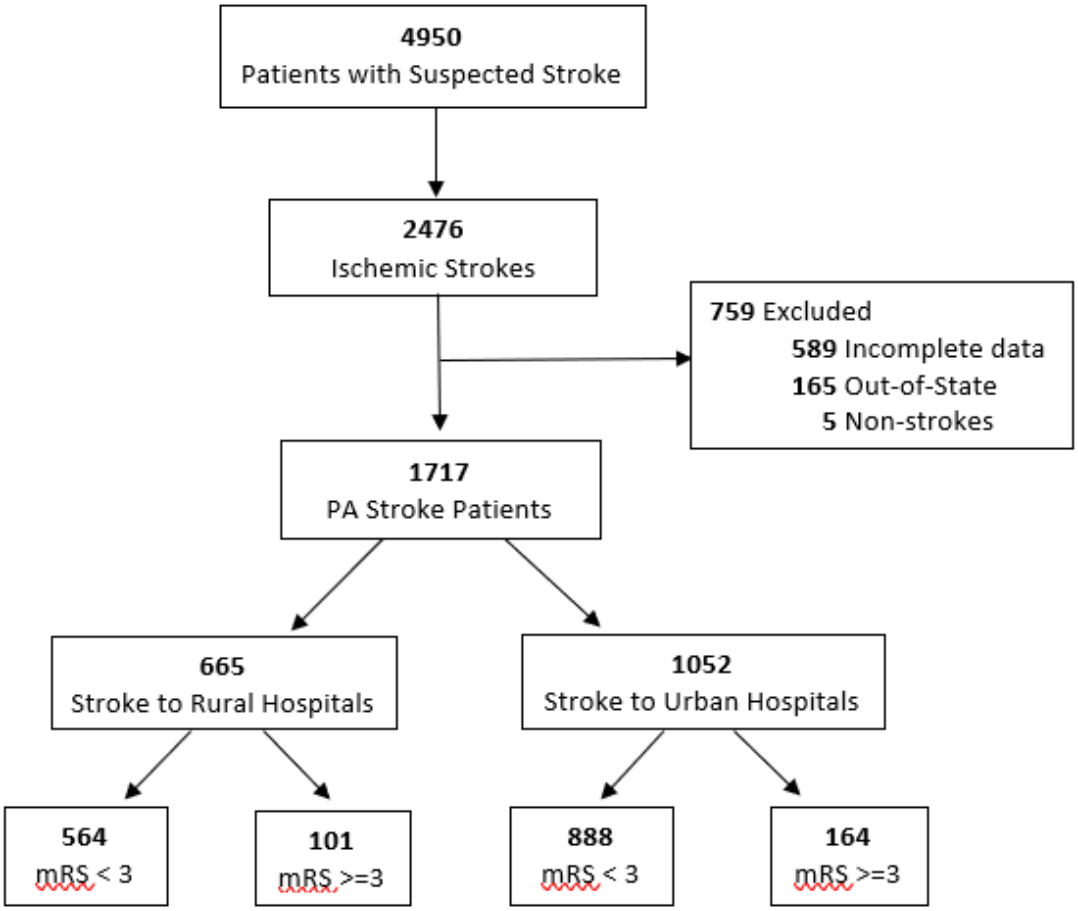


**Figure 2. Consort Diagram for Inclusion/Exclusion of Patients**

### 3.2 Patient Characteristics and Outcome Measures

All patients with stroke-like symptoms that presented to a UPMC facility were included in the original dataset. Clinical chart review was performed to obtain final diagnosis upon hospital discharge (based on ICD-9 and ICD-10 codes), demographic data, functional outcome prior to ED presentation and at discharge, risk factors, NIH Stroke Scale (NIHSS) at ED

presentation and discharge, last known well (symptom duration), intervention use (tPA or ET), and whether the occlusion was a large vessel occlusion (LVO) or not. International Classification of Diseases (ICD) codes were used to obtain a final diagnosis since these codes are used to record and identify specific conditions. We included patients with confirmed ischemic stroke as the final diagnosis in this dataset. The National Institutes of Health Stroke Scale (NIHSS), shown in Table 6, is an assessment tool that measures stroke-related neurologic deficit. It can be used to evaluate stroke severity and can help determine the appropriate treatment for stroke patients.[33] Documentation of a large vessel occlusion (LVO) in the medical records by the physicians was obtained and recorded. LVO included documentation of an occlusion in the Internal Carotid Artery (ICA), Middle Cerebral Artery (MCA), Vertebral Artery, or Basilar Artery.[34]

Extracted medical record data were also used to determine patients' age, race, and sex. Sex and hospital type were coded dichotomously, and race was categorized into two groups: White and Other (includes Black). Hospital location (rural or urban) was defined using the Center for Rural Pennsylvania. Functional outcome was assessed using the modified Rankin Scale (mRS). For this study, baseline mRS was compared to discharge mRS. The score on mRS ranges from normal (0) to death (6), as shown in Table 7. This scale has been used in clinical research and is a common standard for assessing functional outcomes in stroke patients.[8] It measures the degree of dependence or disability in performing daily activities of stroke patients.

### 3.3 Statistical Analysis

Descriptive statistics were determined for demographic factors of age, race, and sex, as well as clinical characteristics such as LVO, tPA, risk factors, admission NIHSS, and discharge NIHSS. Continuous variables were assessed for normal distribution. Since age, admission NIHSS, and discharge NIHSS were all skewed the Wilcoxon Mann-Whitney test was used to compare these variables between rural and urban hospitals. Chi-squared tests were used to compare categorical variables. Fisher's Exact test was used for type of stroke center since it contained cells with less than 5. The p-value for comparisons by type of hospital was not calculated due to no CSCs in a rural setting or ASRs in an urban setting. One-way ANOVA was used to compare continuous measures by type of stroke center. Univariate and multivariable analyses were used to determine factors potentially associated with mRS and mortality. Covariates were adjusted for in the multivariable regression. The association between hospital status with case fatality and mRS were assessed using logistic regression. The mRS was dichotomized due to the clinical cutoff for good functional outcome being mRS< 3 and worse functional outcome as mRS>=3. Statistical analyses were performed using STATA 15.1. P-values <0.05 were considered statistically significant.

# 4.0 Results

## 4.1 Characteristics of Study Population

We reviewed 4,950 patient records with suspected stroke. Figure 2 shows that following exclusion for diagnosis, other than stroke or incomplete data, we included 1,717 patients in the study, 665 (38.7%) were rural communities. The demographic and clinical characteristics for these patients are presented in Table 1. Age showed a left-skewed distribution, with a median age of 74 years (62-83) at admission. In the population, 87.9% patients were white and 48.6% were male. When intervention was assessed, 34.8% of patients received tPA at initial presentation to a hospital. A greater percentage of patients admitted to rural hospitals received tPA at initial presentation as compared to those admitted to urban hospital; 35.3% of patients at a rural hospital and 33.8% at an urban hospital. Of the patients presenting to a rural hospital, 51.6% had LVO and 53.2% of those LVO patients received tPA. Patients presenting to rural hospitals compared to urban hospitals were more likely to be male ($p=0.001$), younger in age ($p<0.0001$), more likely to be white ($p<0.0001$), and have hypertension as a risk factor for stroke ($p=0.042$). Patients presenting to rural hospitals also had a worse NIHSS at admission ($p=0.0001$) and discharge ($p=0.0205$), and had more LVOs ($p<0.0001$) compared to urban hospitals. 60.6% of patients went to a PSC, 22.8% went to a CSC, 0.64% went to an ASR, and 16.0% went to hospital that was not a stroke center. 5.4% of patients received ET at an urban PSC or CSC.

**Table 1. Baseline Demographic and Clinical Characteristics of Ischemic Stroke Patients in Western Pennsylvania 2014-2015**

| | **Total Sample (n=1,717)** | **Rural Hospital (n=665)** | **Urban Hospital (n=1,052)** | **p-value** |
|---|---|---|---|---|
| **Age, median (IQR)** | 74 (62-83) | 71 (60-81) | 75 (63-84) | <0.0001* |
| **Sex, n (%)** | | | | 0.001* |
| **Female** | 883 (51.4) | 308 (46.3) | 575 (54.7) | |
| **Male** | 834 (48.6) | 357 (53.7) | 477 (45.3) | |
| **Race, n (%)** | | | | <0.0001* |
| **White** | 1,510 (87.9) | 620 (93.2) | 890 (84.6) | |
| **Other** | 207 (12.1) | 45 (6.8) | 162 (15.4) | |
| **Risk Factors, n (%)** | | | | |
| **Diabetes** | 537 (31.3) | 226 (34.0) | 311 (29.6) | 0.054 |
| **Hypertension** | 959 (55.9) | 351 (52.8) | 608 (57.8) | 0.042* |
| **Hospital Type, n (%)** | | | | - |
| **PSC** | 1,040 (60.6) | 400 (60.2) | 640 (60.8) | |
| **CSC** | 391 (22.8) | - | 319 (37.2) | |
| **ASR** | 11 (0.6) | 11 (1.7) | - | |
| **Non-Stroke** | 275 (16.0) | 254 (38.2) | 21 (1.9) | |
| **LVO, n (%)** | 773 (45.0) | 343 (51.6) | 430 (40.9) | <0.0001* |
| **NIHSS, median (IQR)** | | | | |
| **Admission** | 9 (4-17) | 12 (5-19) | 9 (4-16) | 0.0001* |
| **Discharge** | 5 (2-13) | 6 (2-14) | 5 (2-12) | 0.0205* |

Abbreviations: NIHSS: National Institute of Health Stroke Scale; LVO: large vessel occlusion; PSC: Primary Stroke Center; CSC: Comprehensive Stroke Center; ASR: Acute-Stroke Ready
*Indicates statistically significant finding based on P<0.05.

### 4.1.1 Main Results

The time from last known well (LKW) to when a patient received tPA at a rural compared to urban hospital was not significantly different (135 vs 133 minutes; p=0.1255). Comparison of time from LKW to presentation at a rural (145 minutes) compared to an urban (123 minutes) hospital was also not significantly different (p=0.9744). However, Table 2 shows

that time from LKW to presentation at the initial hospital did significantly differ (p=0.0382) by type of stroke center. Patients that presented to a CSC arrived within a shorter time interval (120 minutes) than those that presented to a PSC (132 minutes). As expected, the percentage of type of stroke center varied by the hospital location to which a patient presented (Table 2; p<0.0001). The distance from EMS patient pickup to hospital differed by the type of stroke center to which a patient presented (p<0.0001). Of the 665 people presenting to a rural hospital, 32.6% had a severe functional outcome at discharge, while 32.1% of those presenting to an urban hospital had severe functional outcome. Of the 665 people presenting to a rural hospital, the in-hospital mortality rate was 9.3%, while the mortality rate for people presenting to an urban hospital was 7.7%.

Out of 1,717 people, 32.3% had severe functional outcome at discharge. Table 3 depicts factors that were potentially associate with discharge mRS at rural compared to urban hospitals. In this study, we found no association between functional outcome and tPA. Patients who had less severe functional outcome (mRS< 3) at rural centers compared to urban were younger, white males, and were more likely to have LVO. Patients that had a more severe functional outcome (mRS >=3) and presented to a rural hospital were younger, white, and more likely to have a high NIHSS at admission compared to those who presented to an urban hospital.

**Table 2. Characteristics for Ischemic Stroke Patients by Type of Stroke Hospital in Western Pennsylvania 2014-2015**

| | PSC (n = 1,040) | CSC (n = 391) | ASR (n = 11) | Non-Stroke (n = 275) | p-value |
|---|---|---|---|---|---|
| **Hospital Location, n (%)** | | | | | <0.0001* |
| **Rural** | 400 (38.5) | - | 11(100) | 254 (92.4) | |
| **Urban** | 640 (61.5) | 391 (100) | - | 21 (7.6) | |
| **Distance (in miles), median (IQR)** | 5.7 (2.6-10.2) | 10.6 (5.1-31.6) | 13.5 (4.9-22.1) | 3.2 (2-8.7) | <0.0001* |
| **Time from LKW to Initial Hospital, median (IQR), minutes** | 132 (58.5-473) | 120 (70-369) | 96 (32-198) | 151 (53-622) | 0.0382* |
| **Time from LKW to Intervention, median (IQR), minutes** | | | | | |
| **t-PA** | 132 (100-170) | 136 (105-165.5) | 168 (97-175) | 140 (98-186) | 0.4206 |
| **ET** | 181 (154.5-294.5) | 192 (155-420) | - | - | 0.0553 |
| **Time from Hospital Arrival to Intervention, median (IQR)** | | | | | |
| **t-PA** | 60 (41.5-79) | 55.5 (40-72) | 88.5 (65-102.5) | 72 (65.5-90) | 0.0555 |
| **ET** | 105 (96-148) | 80 (64.5-121) | | | 0.0945 |

Abbreviations: LKW: last known well; NIHSS: National Institute of Health Stroke Scale; LVO: large vessel occlusion; tPA: tissue plasminogen activator; ET: endovascular therapy; PSC: Primary Stroke Center; CSC: Comprehensive Stroke Center; ASR: Acute-Stroke Ready

*Indicates statistically significant finding based on P<0.05.

**Table 3. Univariate Analysis of Potential Factors Associated with Functional Outcome in Ischemic Stroke Patients Discharged from UPMC Facility 2014-2015**

| | Functional Outcomes | | | | | |
|---|---|---|---|---|---|---|
| | mRS < 3 (n=1,162) | | | mRS >=3 (n=555) | | |
| | Rural (n = 448) | Urban (n = 714) | P-value | Rural (n = 217) | Urban (n = 338) | P-value |
| **Age, median (IQR)** | 69 (58-79) | 71 (60-80) | 0.045* | 77 (66-85) | 83 (71-89) | <0.001* |
| **Sex, n (%)** | | | <0.001* | | | 0.460 |
| **Female** | 180 (40.2) | 365 (51.1) | | 128 (59.0) | 210 (62.1) | |
| **Male** | 268 (59.8) | 349 (48.9) | | 89 (41.0) | 128 (37.9) | |
| **Race, n (%)** | | | <0.001* | | | 0.028* |
| **White** | 414 (92.4) | 587 (82.2) | | 206 (94.9) | 303 (89.6) | |
| **Other** | 34 (7.6) | 127 (17.8) | | 11 (5.1) | 35 (10.4) | |
| **Risk Factors, n (%)** | | | | | | |
| **Diabetes** | 151 (33.7) | 201 (28.2) | 0.045* | 75 (34.6) | 110 (32.5) | 0.623 |
| **Hypertension** | 225 (50.2) | 404 (56.6) | 0.034* | 126 (58.1) | 204 (60.4) | 0.592 |
| **tPA, n (%)** | 171 (38.2) | 256 (35.9) | 0.426 | 64 (29.5) | 100 (29.6) | 0.981 |
| **LVO, n (%)** | 177 (39.5) | 236 (33.1) | 0.026* | 166 (76.5) | 194 (57.4) | <0.001* |
| **NIHSS, median (IQR)** | | | | | | |
| **Admission** | 8 (4-15) | 6 (3-12) | 0.003* | 20 (13-23) | 15 (9-21) | 0.002* |
| **Discharge** | 3 (1-6) | 3 (1-5) | 0.021* | 19 (13-24) | 17 (11-22) | 0.034* |
| **Hospital Type n, (%)** | | | <0.001* | | | <0.001* |
| **PSC** | 264 (58.9) | 427 (59.8) | | 136 (62.7) | 213 (63.0) | |
| **CSC** | - | 273 (38.2) | | - | 118 (34.9) | |
| **ASR** | 9 (2.0) | - | | 2 (0.9) | - | |
| **Non-Stroke** | 175 (39.1) | 14 (1.9) | | 79 (36.4) | 7 (2.1) | |

Abbreviations: NIHSS: National Institute of Health Stroke Scale; LVO: large vessel occlusion; tPA: tissue plasminogen activator; PSC: Primary Stroke Center; CSC: Comprehensive Stroke Center; ASR: Acute-Stroke Ready

*Indicates statistically significant finding.

Table 4 depicts factors that were potentially associated with in-hospital mortality. A mRS of 6 was used to assess mortality. 8.3% of the patient population had an in-hospital death. We found no association between mortality tPA. Patients who survived to discharge at rural centers compared to urban were younger, more likely to be of white race and male, and were more likely to have LVO and a higher admission NIHSS. Among patients who died in the hospital (mRS=6), those that presented to a rural hospital were younger; no other differences by hospital location were noted. Of those that received ET, 5.6% died.

**Table 4. Univariate Analysis of Potential Factors Associated with In-Hospital Mortality in Ischemic Stroke Patients Discharged from UPMC Facility (2014-2015)**

| | Mortality | | | | | |
|---|---|---|---|---|---|---|
| | mRS<= 5 (n=1,574) | | | mRS=6 (n=143) | | |
| | Rural (n = 603) | Urban (n = 971) | P-value | Rural (n = 62) | Urban (n = 81) | P-value |
| **Age, median (IQR)** | 71 (60-82) | 75 (63-84) | <0.001* | 75 (64-80) | 81 (69-86) | 0.009* |
| **Sex, n (%)** | | | 0.002* | | | 0.204 |
| **Female** | 281 (46.6) | 531 (54.7) | | 27 (43.5) | 44 (54.3) | |
| **Male** | 322 (53.4) | 440 (45.3) | | 35 (56.5) | 37 (45.7) | |
| **Race, n (%)** | | | <0.001* | | | 0.663 |
| **White** | 563 (93.4) | 814 (83.8) | | 57 (91.9) | 76 (93.8) | |
| **Other** | 40 (6.6) | 157 (16.2) | | 5 (8.1) | 5 (6.2) | |
| **Risk Factors, n (%)** | | | | | | |
| **Diabetes** | 205 (33.9) | 287 (29.5) | 0.065 | 21 (33.8) | 24 (29.6) | 0.591 |
| **Hypertension** | 312 (51.7) | 558 (57.4) | 0.026* | 39 (62.9) | 50 (61.7) | 0.887 |
| **tPA, n (%)** | 217 (35.9) | 330 (33.9) | 0.418 | 18 (29.0) | 26 (32.1) | 0.696 |
| **LVO, n (%)** | 291 (48.3) | 366 (37.7) | <0.001* | 52 (83.9) | 64 (79.0) | 0.465 |
| **NIHSS, median (IQR)** | | | | | | |
| **Admission** | 11 (5-19) | 8 (4-15) | <0.001* | 17 (12-22) | 18 (13-26) | 0.542 |
| **Discharge** | 5 (2-12) | 4 (1-10) | 0.066 | 24 (18-27) | 21 (17-26) | 0.309 |
| **Hospital Type n, (%)** | | | <0.001* | | | 0.008* |
| **PSC** | 356 (59.0) | 587 (60.5) | | 44 (70.9) | 53 (65.4) | |
| **CSC** | - | 365 (37.5) | | - | 26 (32.1) | |
| **ASR** | 10 (1.7) | - | | 1 (1.6) | - | |
| **Non-Stroke** | 237 (39.3) | 19 (2.0) | | 17 (27.4) | 2 (2.5) | |

Abbreviations: NIHSS: National Institute of Health Stroke Scale; LVO: large vessel occlusion; tPA: tissue plasminogen activator; PSC: Primary Stroke Center; CSC: Comprehensive Stroke Center; ASR: Acute-Stroke Ready

*Indicates statistically significant finding.

In the multivariable analysis, shown in Table 5, age, LVO presentation, and admission NIHSS scores were predictive of more severe functional outcomes at discharge and higher risk of mortality. Administration of tPA was inversely associated with mRS >=3. Female sex was inversely associated with mortality. Hospital location was not associated with either severe functional outcome or mortality.

**Table 5. Multivariable Model of Factors Associated with Functional Outcome and In-Hospital Mortality at Discharge from a UPMC Hospital (2014-2015)**

| | Functional Outcomes (mRS >=3) (n=555) | | | Mortality (mRS=6) (n=143) | | |
|---|---|---|---|---|---|---|
| | **Crude OR (95% CI)** | **Adjusted OR (95% CI)** | **P-value** | **Crude OR (95% CI)** | **AdjustedOR (95% CI)** | **P-value** |
| **Hospital Location** | | | | | | |
| **Rural** | 1.00 | 1.00 | - | 1.00 | 1.00 | - |
| **Urban** | 0.97 (0.79-1.20) | 1.05 (0.76-1.36) | 0.868 | 0.81 (0.57-1.15) | 0.84 (0.62-1.45) | 0.801 |
| **Age** | 1.04 (1.03-1.05) | 1.05 (1.04-1.06) | <0.001* | 1.01 (1.00-1.02) | 1.02 (1.00-1.03) | 0.028* |
| **Sex** | | | | | | |
| **Male** | 1.00 | 1.00 | - | 1.00 | 1.00 | - |
| **Female** | 1.76 (1.43-2.16) | 1.29 (0.98-1.69) | 0.065 | 0.92 (0.66-1.31) | 0.61 (0.40-0.93) | 0.020* |
| **Race** | 0.56 (0.39-0.79) | 0.72 (0.45-1.12) | 0.152 | 0.53 (0.27-1.01) | 0.41 (0.16-1.05) | 0.063 |
| **Hypertension** | 1.24 (1.01-1.52) | 0.89 (0.68-1.16) | 0.391 | 1.33 (0.94-1.89) | 1.14 (0.76-1.74) | 0.524 |
| **t-PA** | 0.72 (0.58-0.89) | 0.37 (0.28-0.50) | <0.001* | 0.83 (0.58-1.21) | 0.68 (0.45-1.05) | 0.081 |
| **LVO** | 3.34 (2.71-4.13) | 1.67 (1.23-2.28) | 0.001* | 5.99 (3.89-9.21) | 3.48 (2.04-5.95) | <0.001* |
| **Admission NIHSS** | 1.13 (1.12-1.15) | 1.13 (1.11-1.15) | <0.001* | 1.11 (1.08-1.13) | 1.08 (1.05-1.10) | <0.001* |

Abbreviations: NIHSS: National Institute of Health Stroke Scale; LVO: large vessel occlusion; tPA: tissue plasminogen activator; Hospital Location: rural or urban

*Indicates statistically significant finding. P-value is for adjusted OR. Adjusted for age, sex, race, hypertension, tPA, LVO, and admission NIHSS.

## 5.0 Discussion

The objective of this study was to examine factors that may impact functional outcome at discharge and in-hospital mortality of stroke patients presenting to rural versus urban hospitals. Since Western Pennsylvania only has 4 urban counties, we hypothesized that patients presenting to rural centers would have more severe disability and higher mortality rates since the hospitals in those areas may not be equipped to handle stroke, especially patients with LVO.

Our results did not show significant differences in outcome measures between rural and urban hospitals among an integrated health delivery system (UPMC) in Western Pennsylvania. Although the time to administration of tPA did not affect functional outcome or mortality, a factor that did affect functional outcome was whether tPA was administered or not. This is likely due to the fact that although rural hospitals were statistically further from EMS pickup locations, the time to presentation at the hospital did not differ significantly by whether patients presented to a rural versus an urban hospital. Normally, spatial dispersion of hospitals in rural areas would add logistical challenges to timely transportation by ground ambulance services.[17] One potential explanation as to why time to administration was not significant is that access to advanced stroke care may have been provided by telemedicine or through the health systems helicopter service, STAT MedEvac, which can quickly connect isolated patients to hospitals. Thus, stroke patients far from local hospitals could be eligible for air transport by STAT MedEvac to either local hospitals or a tertiary stroke center. Furthermore, patients presenting to local hospitals may be benefitting from the expertise of a stroke neurologist to provide guidance for the administration of tPA or direction to perform rapid transport for catheter-based interventions.

Other patient characteristics that predicted worse functional outcomes and mortality were older age, higher admission NIHSS scores, and LVO. Rural hospitals tended to have more LVO and higher admission NIHSS scores. This is likely spectrum bias and confounding by indication as those patients were more likely to require an intervention or interfacility transfer between hospitals. Patients with LVO tend to have more complex strokes or larger occlusions which can lead to higher NIHSS scores. The higher the NIHSS score, the more impaired a stroke patient is. Patients with LVO were 1.67 times more likely to have a severe disability at discharge and 3.48 times more likely to have a greater risk of mortality.

Of the 610 patients that initially presented to a rural hospital, almost all of them (99.5%) were subsequently transferred to urban hospitals for further care. Patients presenting to rural hospitals and diagnosed with LVO may be transported to a CSC for higher level care, which would explain why rural centers had more LVOs and higher NIHSS scores at admission than urban centers, yet no difference in functional outcomes. Since rural hospitals often lack resources for larger strokes, such as stroke interventionalists, LVO patients are typically transferred to CSCs. The average time to ET was 192 (155-420) minutes, but of the 774 LVO patients, only 11.8% received ET. This is similar to other studies found that only a small minority of stroke patients (< 5%) receive ET.[12] Worse clinical outcomes may be higher in CSCs due to sicker patients being transported to those facilities given that they can handle more complex cases. This is a major confounder as the populations that stay at rural hospitals, or are transferred, may be substantially different in ways that were not measured.

The fact that there were no significant differences in functional outcomes or mortality between rural and urban centers could indicate that this hospital system has deployed a system of care capable of providing adequate stroke care interventions, or that transfer protocols is

correctly controlling for differences in patient populations. Additionally, PSCs and ASRs without stroke specialists may be utilizing telemedicine to contact hospitals with specialists to help diagnose patients with stroke-like symptoms, define treatment options, and identify patients in need for rapid transfer. Previous studies have suggested that telemedicine may be the only option for extremely remote rural areas in which long distance would not allow for transporting the patient in a timely manner.[17] Contrary to other studies, our study found that there was a higher in-hospital mortality rate for patients discharged from an urban (12.2%) compared to rural hospital (9.3%).[19]

A strength of our study was the methodology used to obtain data. Extracting data directly from medical records reduced the likelihood of misclassification or reporting bias. These data include a large sample size and cover a broad range of patients and provider types improving the generalizability of the findings. Further, there are not many focused epidemiological studies of ischemic stroke patients with LVO in rural compared to urban areas. Our study is novel and contributes to the literature since it is one of the only studies of its kind to be done in Western Pennsylvania.

Our study has some limitations worth noting, though. This study only used a portion of the data available due to the complexity of manual data extraction. Also only represents patients that were taken to a UPMC facility. Follow-up data was not collected as some patients did not return to a UPMC facility, and long-term outcomes may be more indicative of quality of acute care. We also could not include all the risk factors for stroke we collected (atrial fibrillation, anticoagulant use, and prior stroke history) since that data was incomplete. Further research is needed to determine whether interhospital transfer impacts patient outcomes at discharge.

This multi-center retrospective study demonstrates that stroke patients discharged from UPMC rural hospitals do not have worse functional outcomes or higher mortality than patients discharged from UPMC urban hospitals in Western Pennsylvania. Though these hospitals are less equipped to handle complex strokes, they are still able to provide adequate acute stroke management. Many rural hospitals are being certified to become PSCs thus, patients can be stabilized before transfer to a tertiary facility.[15] Overall, further analysis of the entire study population may provide more insight into the differences between rural and urban stroke management.

## Appendix Supplementary Tables and Figures

**Table 6. A Simplified Version of the NIH Stroke Scale Evaluation Form**

| Category | Description | Score |
|---|---|---|
| 1a. Level of Consciousness (LOC)<br>(Alert, drowsy, etc.) | 0 = Alert<br>1 = Drowsy<br>2 = Stuporous<br>3 = Coma | |
| 1b. LOC Questions<br>(Month, age) | 0 = Answers both correctly<br>1 = Answers one correctly<br>2 = Incorrect | |
| 1c. LOC Commands<br>(Open/close eyes, make fist/let go) | 0 = Obeys both correctly<br>1 = Obeys one correctly<br>2 = Incorrect | |
| 2. Best Gaze<br>(Eyes open – patient follows examiner's finger or face) | 0 = Normal<br>1 = Partial gaze palsy<br>2 = Forced deviation | |
| 3. Visual Fields<br>(Introduce visual stimulus/threat to patient's visual field quadrants) | 0 = No visual loss<br>1 = Partial Hemianopia<br>2 = Complete Hemianopia<br>3 = Bilateral Hemianopia (Blind) | |
| 4. Facial Paresis<br>(Show teeth, raise eyebrows and squeeze eyes shut) | 0 = Normal<br>1 = Minor<br>2 = Partial<br>3 = Complete | |
| 5a. Motor Arm – Left<br>5b. Motor Arm – Right<br>(Elevate arm to 90$^{o}$ if patient is sitting, 45$^{o}$ if supine) | 0 = No drift<br>1 = Drift<br>2 = Can't resist gravity<br>3 = No effort against gravity<br>4 = No movement<br>X = Untestable (Joint fusion or limp amp) | |
| 6a. Motor Leg – Left<br>6b. Motor Leg – Right<br>(Elevate left 30$^{o}$ with patient supine) | 0 = No drift<br>1 = Drift<br>2 = Can't resist gravity<br>3 = No effort against gravity<br>4 = No movement<br>X = Untestable (Joint fusion or limp amp) | |
| 7. Limb Ataxia<br>(Finger-nose, heel down shin) | 0 = No ataxia<br>1 = Present in one limb<br>2 = Present in two limbs | |

**Table 6 Continued**

| | | |
|---|---|---|
| 8. Sensory<br>(Pin prick to face, arm, trunk, and leg – compare side to side) | 0 = Normal<br>1 = Partial loss<br>2 = Severe loss | |
| 9. Best Language<br>(Name item, describe a picture and read sentences) | 0 = No aphasia<br>1 = Mild to moderate aphasia<br>2 = Severe aphasia<br>3 = Mute | |
| 10. Dysarthria<br>(Evaluate speech clarity by patient repeating listed words) | 0 = Normal articulation<br>1 = Mild to moderate slurring of words<br>2 = Near to unintelligible or worse<br>X = Intubated or other physical barrier | |
| 11. Extinction and Inattention<br>(Use information from prior testing to identify neglect or double simultaneous stimuli testing) | 0 = No neglect<br>1 = Partial neglect<br>2 = Complete neglect | |

**Table 7. Modified Rankin Scale (mRS)**

| Score | Definition |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability; able to carry out all usual duties and activities |
| 2 | Slight disability; unable to carry out previous activities, but can look after oneself without assistance |
| 3 | Moderate disability; requires some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk and attend to bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent, requiring constant nursing care and attention |
| 6 | Dead |

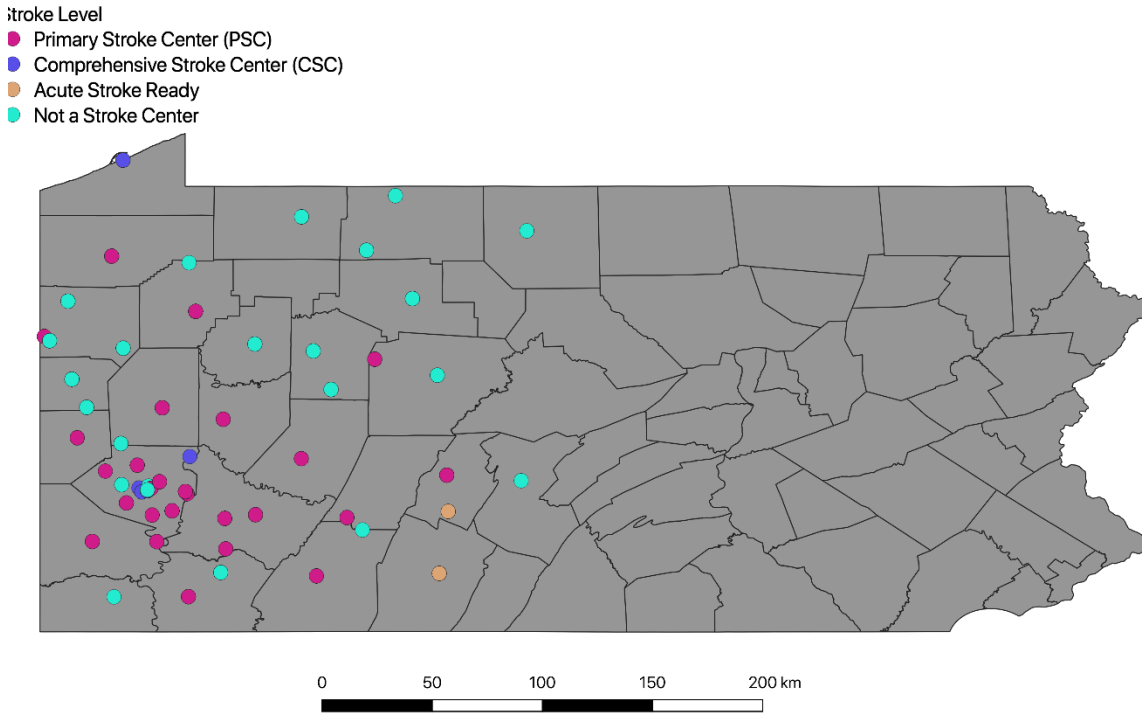


**Figure 3. Type of Stroke Centers in Western Pennsylvania**

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