eNeurologicalSci 21 (2020) 100285

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: www.elsevier.com/locate/ensci

Factors affecting time between symptom onset and emergency department arrival in stroke patients

Scott M. Le, DO [a,b,c,*], Laurel A. Copeland, PhD [d,e], John E. Zeber, PhD [f], Jared F. Benge, PhD [b,c], Leigh Allen, MSN [b,g], Jinmyoung Cho, PhD [i], I-Chia Liao, MPH [i], Jennifer Rasmussen, MD [b,c]

[a] Duke Health, Department of Neurology, Division of Vascular Neurology and Stroke, 40 Duke Medicine, Circle, Durham, NC 27710, United States of America
[b] Baylor Scott & White Health, Department of Neurology, 2401 S 31st Street, Temple, TX 76508, United States of America
[c] Texas A&M Health Science Center College of Medicine, 8447 Bryan Rd, Bryan, TX 77807, United States of America
[d] VA Central Western Massachusetts, 421 N Main St, Leeds, MA 01053, United States of America
[e] University of Massachusetts Medical School, Department of Population and Quantitative Health Sciences, 55 N Lake Ave, Worcester, MA 01655, United States of America
[f] University of Massachusetts at Amherst, School of Public Health & Health Sciences, Health Policy & Management, 300 Massachusetts Ave, Amherst, MA 01003, United States of America
[g] Ascension Seton, 1201 West 38th St, Austin, TX 78705, United States of America
[h] Baylor Scott & White Health, Center for Applied Health Research, 4236 Lowes Dr., Temple, TX 76502, United States of America

ARTICLE INFO

Keywords:
Stroke care
Acute stroke
Stroke, ischemic
Access to care
Prehospital delay

ABSTRACT

Background and purpose: Delays in seeking care compromise diagnosis, treatment options, and outcomes in ischemic strokes. This study identified factors associated with time between stroke symptom onset and emergency department (ED) arrival at a private nonprofit medical center serving a large rural catchment area in central Texas, with the goal of identifying symptomatic, demographic, and historical factors that might influence seeking care.

Methods: Demographic and clinical data from a large tertiary care center's Get With The Guidelines (GWTG) database were evaluated in 1874 patients presenting to the ED with a diagnosis of transient ischemic attack (TIA), intracranial hemorrhage, subarachnoid hemorrhage, or ischemic stroke. The dependent variable was time between discovery of stroke symptoms and presentation at the hospital (time-to-ED). Factors entered into regression models predicting time-to-ED within 4 h or categorical time-to-ED.

Results: The average time from symptom onset to presentation was 15.0 h (*sd* = 23.2), with 43.6% of the sample presenting within 4 h of symptom onset. Results suggested that female gender (Odds Ratio [OR] = 0.70; 95% Confidence Interval [CI] 0.23–0.74), drug abuse (OR = 0.41; CI 0.23–0.74), and diabetes were significantly associated with longer time to presentation.

Conclusions: A combination of demographics, stroke severity, timing, and health history contributes to delays in presenting for treatment for ischemic stroke. Stroke education concentrating on symptom recognition may benefit from a special focus on high-risk individuals as highlighted in this study.

1. Introduction

Stroke is a devastating disease that affects an estimated 7 million people in the United States with 795,000 new or recurrent cases every year. Intravenous tissue plasminogen activator (tPA) and endovascular thrombectomy are both time-sensitive treatments with proven benefit in patients with acute ischemic strokes [1,2]. Current guidelines suggest that tPA can be utilized up to 4.5 h after symptom onset and endovascular thrombectomy up to 24 h after symptom onset [3,4]. Despite the availability of these interventions, the national average tPA usage rate is only 5–6% [5,6] and less than 1% for endovascular thrombectomy [7]. The most common reason for exclusion from acute treatment is arrival to ED outside of the designated time window [8].

Despite the importance of reducing time to presentation for

* Corresponding author at: Duke Health, Department of Neurology, Division of Vascular Neurology and Stroke, 40 Duke Medicine, Circle, Durham, NC 27710, United States of America.
E-mail address: scott.le@duke.edu (S.M. Le).

https://doi.org/10.1016/j.ensci.2020.100285
Received 19 March 2020; Received in revised form 21 August 2020; Accepted 20 October 2020
Available online 24 October 2020

treatment of stroke, research into specific factors associated with delayed presentation has revealed varied results. There is some preliminary evidence to suggest that factors such as race [9,10] and gender [10] may influence time to presentation, but in our clinical experience, other factors such as comorbidities that may have fluctuating symptoms as a part of a disease state, time of day of symptom onset, and distance from the hospital may all influence patient arrival times to the ED. In addition, prior studies have highlighted factors such as stroke severity or symptoms [11], along with ethnicity and sex [10], as meaningfully related to delayed ED presentation. A systematic review [12] highlighted this lack of recognition of stroke symptoms as a primary driver of delays to treatment for TIAs. Less frequently addressed in the literature to date are factors such as health insurance and other medical comorbidities which may also drive patient and family decision making. For example, individuals concerned about the cost of care may delay arrival to the ED secondary to fear of cost/expense in related conditions such as heart attack [13]. Furthermore, patients with other conditions that can have a fluctuating course or are associated with non-specific neurological signs such as confusion may be more prone to avoid seeking care if the presenting symptom is similar to those experienced previously [14]. From a population health standpoint, identifying individuals both at risk for stroke and at risk for delaying care may help identify more focused educational and other interventions to reduce the personal and financial burden of stroke.

The current study sought to 1) identify demographic, health insurance, stroke symptom, and medical comorbidity factors that differed between those presenting within and outside of recommended treatment windows for acute stroke for the catchment area of the health system studied; 2) identify variables most strongly predictive of "near misses" to the recommended treatment window; and 3) provide data from a comprehensive stroke center that takes care of a large catchment area encompassing a largely rural population with otherwise limited access to healthcare.

2. Methods

We conducted a retrospective review of Get With The Guidelines data from our local institution, a single hospital within a large integrated healthcare system, for all stroke cases from January 2015–July 2017. Details of the nationwide GWTG registry can be found elsewhere [15,16]. To be included in the study, individuals needed to present to the ED within 7 days of symptom onset and subsequently be diagnosed with transient ischemic attack, ischemic stroke, cerebral hemorrhage, or subarachnoid hemorrhage.

The dependent variable, time to ED presentation, was calculated as the difference from time of presentation at ED and time of symptom discovery. We evaluated this outcome in two ways. In the first, we grouped patients who presented within 0–4 h (within the established tPA window) versus later presentation (outside the tPA window). Because individuals who are "near misses" to the tPA window or are within the slightly longer thrombectomy window may comprise further populations of interest, an ordinal dependent variable was also created with 0 to <4, 4 to <8, 8 to <24, 24 to <48, and 48–168 (i.e. 2–7 days) hours as the categorization.

Covariates included demographics, stroke symptoms and severity, medical comorbidities, and timing of symptom onset (day of week; time of day). Demographic variables included age categorized as 65+ versus younger, gender, race/ethnicity, and rural versus urban residence. Rural versus urban categorization was made based upon ZIP code of patient recoded to Rural-Urban Commuting Area (RUCA [17]), then dichotomized. Insurance status was identified as self-pay (uninsured), Medicaid, versus commercial insurance program or Medicare. Medical comorbidities that are associated with increased stroke risk or might mimic stroke were abstracted from GWTG, including atrial fibrillation and flutter, carotid stenosis, prior myocardial infarct (MI), prosthetic heart valve, peripheral vascular disease, diabetes, dyslipidemia, heart failure, migraine, obesity, pregnancy, renal disease, sleep apnea, drug or alcohol disorder, depression, smoking history, and family history of stroke. Stroke features analyzed included history of prior stroke of any type, initial stroke severity grouped as categories based upon initial NIHSS scale (>15, 5–15, <5), similar to the categorization used in Messé et al. 2016 [18], and, for descriptive purposes, specific symptoms such as the presence of weakness, altered state of consciousness, aphasia, or other neurological signs, were explored, though not all of these symptoms were routinely calculated. Time of day when the stroke occurred was categorized as waking hours (07:00 to 21:00) and non-waking hours (21:00–07:00). The hour of midnight was assigned by GWTG to any date of symptom onset for which the actual time was unknown; this frequently occurs when the actual date is uncertain. Weekends were distinguished from weekdays. GWTG collects whether Emergency Medical Services (EMS) were notified in advance of arrival at the ED.

In the first step of our analyses, we analyzed bivariate associations with time-to-ED of factors chosen from the domains of demographics, medical system, onset of symptoms, and comorbidity. Independent variables were then entered into multivariable regression models predicting time to ED. Logistic models regressed the demographic and clinical measures on the dichotomy of presentation to ED within the 4 h tPA window, while ordered multinomial regression analyzed the 5-level measure of time-to-ED. Results are reported as odds ratios with their 95% confidence intervals (OR; 95% CI). Risk factors for delayed presentation were those with odds ratios less than 1 with the 95% CI excluding 1.0, while odds ratios greater than 1 identified protective factors. Weak (OR > 1 to 2 or 0.5 to <1) effects were noted as well as moderate or stronger effects (OR > 2 or < 0.5) [19]. The c-statistic assessed goodness-of-fit of the logistic regression model on a scale ranging from 0.50, no better than chance, to 1.0, a perfect fit. SAS 9.4 generated all analytic results (© SAS Institute, Cary, NC).

This retrospective study was reviewed and approved by our local institutional review board. Consent was not required as all information within the GWTG registry was de-identified. This work represents the authors' independent analysis of local or multicenter data gathered using the American Heart Association (AHA) Get With The Guidelines® Patient Management Tool but is not an analysis of the national GWTG dataset and does not represent findings from the AHA GWTG National Program.

3. Results

We reviewed 1874 stroke cases that presented to our institution within 1 week of symptom onset, between January 2015 and July 2017. Descriptive data for the sample is found in Table 1. The study cohort was predominantly older (58% over age 65) and white (82%) and evenly split by gender. 11% of the cohort was uninsured and 2% were on Medicaid. Approximately half of patients presented during waking hours, and 27% of patients presented on the weekend. Advanced EMS notification was initiated on 1 in 4 patients. Most patients had a low initial National Institute of Health Stroke Scale (NIHSS), although 26% scored between 5 and 15 and 11% scored above 15. Patient comorbidities on presentation included hypertension (78%), diabetes (31%), prior stroke (25%), smoker (20%), atrial fibrillation (14%), obesity (12%), and substance abuse (5%) among others. These characteristics for patients with timely arrival and those arriving 4 or more hours post-stroke are shown in Table 2.

As to our primary outcome of interest, less than half of patients (43%) presented to the ED within 4 h of symptom recognition based on patient or companion report. Of the individuals that presented outside this timeframe, 13% could be considered "near misses" for tPA eligibility as they arrived for care 4 to 8 h after symptom onset. Another 25% presented 8–24 h after symptoms were identified, conceivably within the window of mechanical thrombectomy. Fully 18% presented one or more days after symptom onset. Our tPA administration rate was 10% while our thrombectomy rate was 4%.

Table 1
Descriptive and bivariate summary of study cohort characteristics.

Variable name	Mean (SD, Min, Max) or Frequency (%)
Demographics	
Age	67.5 (14.7, 18, 102)
Age ≥ 65	1104 (58.9%)
Gender	
Female	944 (50.4%)
Male	928 (49.6%)
Race	
White	1392 (82.5%)
Non-White	296 (17.5%)
Location	
Rural location	175 (9.5%)
Urban location	1671 (90.5%)
Insurance	
Commercial insurance	716 (38.2%)
Medicare	1003 (53.5%)
Medicaid	33 (1.8%)
No insurance/ self-paid	209 (11.2%)
Time from symptom onset to ED	
Less than 4 h	818 (43.7%)
From 4 to <8 h	249 (13.3%)
From 8 to <24 h	476 (25.4%)
From 1 to 2 days	184 (9.8%)
From 3 to 7 days	147 (7.8%)
Advance EMS notification	467 (24.9%)
Time admitted	
Waking hours (7 am – 9 pm)	938 (50.0%)
Non-waking hours (9 pm-7 am)	936 (50.0%)
Stroke Symptoms and Medical Comorbidities	
National Institute of Health Stroke Scale (NIHSS)[a]	
NIHSS initial score (mean; SD; range 0–42)	5.7 (SD: 7.4)
NIHSS less than 5	1084 (62.5%)
NIHSS between 5 and 15	451 (26.0%)
NIHSS greater than 15	199 (11.5%)
Prior stroke	467 (24.9%)
Atrial fibrillation or flutter	262 (14.0%)
CAD / prior MI	427 (22.8%)
Diabetes	582 (31.0%)
Hypertension	1469 (78.4%)
Dyslipidemia	947 (50.5%)
Sleep apnea	140 (7.5%)
Obesity	228 (12.2%)
Smoker	378 (20.2%)
Substance abuse	90 (4.8%)

[a] 140 cases missing data.

Table 2
Characteristics from get with the guidelines on stroke by arrival at ED within 4 hours versus longer than 4 hours ($n = 1874$).

Characteristic	Within 4 h		More than 4 Hours	
	n	%	n	%
Age 65 or older	509	62.2	595	56.3
Female	395	48.3	549	52.1
Minority	193	23.6	288	27.3
Rural	64	7.8	111	10.5
Urban	739	90.3	932	88.3
Commercial insurance	318	38.9	398	37.7
Medicare	445	54.4	558	52.8
Medicaid	8	1.0	25	2.4
Uninsured/self-pay	81	9.9	128	12.1
Advance Notification from EMS	259	31.7	208	19.7
Waking Hours	633	77.4	305	28.9
Weekend	207	25.3	303	28.7
NIHSS was done	773	94.5	961	91.0
NIHSS <5	428	55.4	656	68.3
NIHSS 5–15	219	28.3	232	24.1
NIHSS >15	126	16.3	73	7.6
Initial Exam: Weak	59	7.2	75	7.1
Initial Exam: Altered Consciousness	30	3.7	51	4.8
Initial Exam: Aphasia	44	5.4	46	4.4
Stroke Time Known	468	57.2	132	12.5
Prior Stroke	190	23.2	277	26.2
Atrial fibrillation/flutter	137	16.7	125	11.8
CAD / Prior MI	171	20.9	256	24.2
Carotid Stenosis	16	2.0	17	1.6
Diabetes	236	28.9	346	32.8
Peripheral vascular disease	24	2.9	44	4.2
Hypertension	654	80.0	815	77.2
Dyslipidemia	417	51.0	530	50.2
Heart Failure	84	10.3	100	9.5
Renal disease	41	5.0	66	6.3
Migraine	36	4.4	50	4.7
Sleep Apnea	66	8.1	74	7.0
Prosthetic Heart Valve	78	9.5	66	6.3
Family History of Stroke	79	9.7	98	9.3
Depression	120	14.7	134	12.7
Drug/Alcohol disorder	23	2.8	67	6.3
Smoker	139	17.0	239	22.6
Obese	100	12.2	128	12.1
Pregnant	1	0.1	4	0.4

In the logistic regression model predicting presentation within 4 h of symptom onset (Table 3), female gender (OR = 0.70; 95%CI 0.55–0.89), Medicaid status (OR = 0.22; 0.07–0.64), diabetes (OR = 0.72; 0.56–0.93), smoker (OR = 0.71; 0.53–0.96), rural residence (OR = 0.66; 0.44–0.99) and substance abuse (OR = 0.41; 0.23–0.74) were significantly associated with presenting outside the therapeutic window; fit was good (c-statistic = 0.80). Conversely, higher NIHSS scores and advance notice from EMS correlated with more prompt presentation, and symptom onset during waking hours was the strongest predictor of presentation within the therapeutic window (OR = 8.7; 6.9–11.0).

Higher NIHSS was associated with a higher likelihood of presenting within four hours of symptom onset, as there was about 4% increased relative odds of the outcome of timely presentation for each single-point increase in the NIHSS. When we grouped patients based on NIHSS (results not shown), patients with NIHSS between 5 and 15 were more likely to present within four hours of symptom onset compared to patients with lower NIHSS (OR 1.38; 1.06–1.79). Having even higher NIHSS of greater than 15 was associated with more than doubled odds of arriving within four hours of symptom onset (OR 2.49; 1.70–3.64).

In the ordered logistic regression comparing four discrete intervals to presenting within four hours (Table 4), we noted that females were more likely to present later (4 to 8 and 8 to 24 h after onset). Patients with diabetes were more likely to present 8 to 24 h and had doubled odds of presenting 48–168 h after symptom onset. A history of substance abuse was associated with arrival time outside the therapeutic window (all categories 8 h through 7 days after onset), and Medicaid patients had 4 or more times the odds of presenting late (all categories 4 h through 7 days after onset). Factors associated with more timely presentation (<4 h from symptom onset) included higher NIHSS score, onset during workdays or waking hours and having advance EMS notification. Surprisingly, obesity seemed to be protective as well, as those patients were more likely to present within four hours of symptom onset compared to the 4-to-8-h group.

4. Discussion

The current analyses identified several factors associated both with timely access of care as well as features that increase the odds of delayed or near misses of presentation within the therapeutic window in 1874 stroke cases arriving at a large not-for-profit regional medical center. These protective and risk factors are considered in turn below.

4.1. Protective factors: time of day of symptom onset and advanced notification

Patients with stroke symptoms that occurred or were recognized during waking hours were more likely to present to the ED for evaluation within 4 h compared to patients that had symptom onset during the nighttime hours. This was expected as stroke symptoms that occur

Table 3
Logistic regression model results predicting presentation delay of 4 or more hours among 1734 Southwestern patients with stroke onset within prior 7 days.

Characteristic	Odds ratio	95% CI
Female	0.70[a]	0.55–0.89
Age 65 or older	1.09	0.83–1.43
Minority race/ethnicity	0.86	0.65–1.14
Medicaid	0.22[a]	0.07–0.64
Uninsured	0.89	0.61–1.32
Advance Notification from EMS	1.75[a]	1.34–2.29
NIHSS initial score (range 0–42)	1.04[a]	1.03–1.06
Atrial fibrillation or flutter	1.20	0.85–1.69
Coronary artery disease or prior MI	0.82	0.62–1.10
Carotid Stenosis	1.39	0.59–3.26
Diabetes	0.72[a]	0.56–0.93
Peripheral Vascular Disease	0.83	0.43–1.60
Hypertension	1.14	0.85–1.53
Dyslipidemia	0.95	0.74–1.22
Heart failure	0.97	0.65–1.46
Renal disease	1.08	0.65–1.79
Migraine	1.24	0.72–2.15
Sleep Apnea	1.07	0.69–1.66
Prior stroke	0.86	0.66–1.12
Prosthetic Heart Valve	1.20	0.79–1.81
Family history of stroke	1.01	0.70–1.47
Depression	1.15	0.82–1.61
Drug or alcohol disorder	0.41[a]	0.23–0.74
Tobacco use	0.71[a]	0.53–0.96
Obesity	1.30	0.90–1.87
Rural residence	0.66[a]	0.44–0.99
Onset on weekend	0.82	0.63–1.06
Onset during waking hours (7 am-9 pm)	8.73[a]	6.92–11.02

[a] Indicates 95% CI excludes 1.

Table 4
Ordered logistic model results predicting categories of presentation delay among 1734 Southwestern patients with stroke onset within prior 7 days.

Characteristic[a]	OR (4- < 8 h)	OR (8- < 24 h)	OR (1- < 2 days)	OR (2–7 days)
Female	1.70[a]	1.45[a]	1.03	0.98
Age 65 or older	0.91	0.97	0.82	0.95
Minority race/ethnicity	1.19	1.16	1.04	1.30
Medicaid	4.86[a]	4.44[a]	4.70[a]	6.77[a]
Uninsured	1.03	1.32	1.09	0.88
Advance Notification from EMS	0.65[a]	0.52[a]	0.65	0.39[a]
NIHSS initial score (range 0–42)	0.96[a]	0.98	0.93[a]	0.89[a]
Atrial fibrillation or flutter	0.80	0.86	0.69	0.93
Coronary artery disease or prior MI	1.25	1.45[a]	0.66	1.09
Carotid Stenosis	0.60	0.71	1.04	0.67
Diabetes	1.23	1.45[a]	1.40	2.01[a]
Peripheral Vascular Disease	1.48	1.22	1.00	0.81
Hypertension	0.78	0.98	1.07	0.67
Dyslipidemia	0.98	1.11	1.32	0.76
Heart failure	0.86	1.11	1.24	1.00
Renal disease	0.72	0.93	1.36	0.92
Migraine	0.89	0.79	0.48	0.89
Sleep Apnea	1.20	0.87	0.84	0.60
Prior stroke	1.17	1.20	1.18	0.91
Prosthetic Heart Valve	1.02	0.80	0.58	0.62
Family history of stroke	0.99	0.96	1.02	1.18
Depression	0.88	0.81	0.99	0.94
Drug or alcohol disorder	1.54	2.93[a]	3.17[a]	5.23[a]
Tobacco use	1.37	1.34	1.43	1.64
Obesity	0.49[a]	0.86	0.89	1.39
Rural residence	1.72[a]	1.29	1.52	1.60
Onset on weekend	1.06	1.27	1.34	1.69[a]
Onset during waking hours (7 am-9 pm)	0.55[a]	0.08[a]	0.05[a]	0.01[a]

[a] Indicates 95% CI excludes 1. Complete results available upon request.

during sleep tend to have a delayed presentation given that the last time known well was assumed to be prior to sleep. While stroke onset that occurs during sleep may not be considered a modifiable factor per se, for some patients education on so called "wake-up stroke" symptoms and the need for timely presentation even with these symptoms is warranted [20,21]. The wake-up stroke population tends to fall in the 8-to-24 h group as these are the patients with a last known well time of the previous evening. While select patients can potentially qualify for mechanical thrombectomy [3,4], there is emerging evidence that some of these wake-up strokes can also potentially qualify for tPA administration [21]. This further highlights the importance of presenting to an ED as quickly as possible, even in the setting of a wake-up stroke with a prolonged last known well. At a system level, continuing to work with frontline emergency personnel to aggressively work up wake-up stroke patients in an age of thrombectomy is also encouraged.

Patients who notified EMS were also more likely to present within 4 h than patients without advance EMS notification. EMS provider education to recognize stroke symptoms and notify the ED is critical as hospitals try to expedite door-to-needle tPA times [22]. Healthcare systems that maintain their own EMS crews may potentially also have an advantage to this end, as clear education on symptom recognition and immediate management can be provided in a systematic way. These features were indeed present in our current setting. That being said, as only 25% of our sample utilized EMS, opportunity remains for educating patients, community providers, and broader EMS networks on the importance of utilizing emergency services when a stroke is suspected. Patient education by the healthcare system or health insurance provider could have a positive cost-benefit profile; future research should examine this possibility, as community interventions to date have had disappointing results [23].

4.2. Risk factors for missing the tPA window: demographics, subtle symptoms, and stroke mimics

Women with stroke tend to have more severe stroke symptoms and poorer prognosis overall [24]. One reason for the worse prognosis may be delayed treatment (as evidenced in the current study). Our study supports prior literature by highlighting that women were more likely to miss presenting to the ED within the time therapeutic window. Women may be more likely to discount their own health needs, or their family may be used to relying on the woman to advocate for pursuing medical care, leaving the woman herself without a "health protector" [25–29]. Coupled with evidence that females overall were less likely to be treated with tPA even when presenting promptly to the ED [18], addressing delays to presentation and treatment may be a very important avenue to explore to reduce female stroke morbidity and mortality.

As having a stroke may prevent the patient from initiating treatment, it may fall upon caregivers to recognize symptoms and initiate treatment-seeking. In our patient population, oftentimes spouses are the ones making this initial evaluation. Future research understanding what leads caregivers to initiate or wait on initiating care is warranted to help identify barriers to timely care. Studies have suggested that women are better than men at recognizing stroke symptoms and are also more likely to activate EMS in the setting of acute stroke symptoms [30], so women's male partners in particular may need education to improve recognition and initiation of treatment not just for themselves, but also for their spouses.

In addition to gender, patients with diabetes and substance abuse as well as smokers were more likely to present outside of the 0 to 4 h time window. One potential reason to account for delayed presentation could be that diabetic patients may experience symptoms similar to indicators of stroke when they are hypoglycemic or hyperglycemic. Thus, patients may defer prompt evaluation and opt for waiting to see if their symptoms improve with either food or insulin. Similarly, individuals with substance abuse may have periods of isolated confusion or other neurological symptoms that mask or could be mistaken for stroke

symptoms. Substance abuse populations also have multiple other barriers to accessing care, such as being hesitant to present for medical evaluation or having smaller social networks that may preclude activation or advice to seek care.

Other comorbidities such as cardiovascular disease and prior history of stroke or TIA were not associated with reduced time of presentation from symptom onset. Stroke education is provided to patients and their caregivers upon discharge at our facility for those diagnosed with cardiovascular disease and stroke, which raises the question of how effective such education is for these patient populations; the timing of stroke education may need to be later than at discharge, when patients are focused on transitioning from the hospital and potentially overwhelmed with information. Patients and their caregivers should be more vigilant about potential new stroke symptoms – since we did not see an association between prior strokes and presenting within 4 h of symptom onset, it suggests that there may be additional barriers preventing patients from presenting for evaluation in a timelier manner.

There was no difference seen in timeliness of presentation in patients with dyslipidemia or hypertension, two prominent risk factors for stroke [19]. In our cohort, 78% of stroke patients carried a prior diagnosis of hypertension, with 51% having a prior diagnosis of dyslipidemia. These patient populations and their caregivers would make ideal target groups for stroke education, which may be done upon initial diagnosis of hypertension or dyslipidemia, as well as reinforcement of stroke education on subsequent follow-up visits in the primary care setting.

Higher (worse) NIHSS values were associated with more timely presentations to the ED. More severe symptoms, which are usually more alarming and noticeable to patients and their caregivers, prompt immediate responses in many cases. Conversely, patients with milder symptoms may be slow or reluctant to recognize the seriousness of their symptoms, and thus tend to delay their presentation to the ED. Education with an emphasis on milder symptoms such as sensory changes or dysarthria may help to reduce the time from symptom onset to presentation to the ED. We attempted to look at different presenting symptom types such as weakness, sensory changes, or aphasia, but the data regarding symptom types was not consistently recorded. Different presenting symptoms could potentially influence whether a patient seeks medical attention as some symptoms are more obvious or recognizable than others.

Although our sample size for patients in rural areas was small, there were somewhat more patients in this subgroup that arrived within the 0-to-4 h time window (63% of rural patients arrived after 4 h vs 56% of urban patients; $p < .05$; data not shown), which would be in the "near miss" category for tPA administration. Additional attention to these rural populations in the form of stroke education for residents and the value of ED notification for EMS can help to shift these "near misses" to the earlier time window where tPA can potentially be safely administered.

4.3. Limitations

Sufficient data were not available on type of symptom and location of stroke. Our stroke patients were younger than national averages with 42% under age 65 versus 34% <65 nationally [31]. Our center is in a unique setting, being the largest medical center covering a primarily rural area over 25,000 mile^2 in central Texas, limiting ability to generalize the trends seen in this study to other settings. Future studies could expand on the current results by identifying the potential barriers and health decision-making factors predominating in high-risk individuals and their caregivers for missing stroke therapeutic windows. As these and other potential barriers continue to be explored, interventions tailored to a particular healthcare system can be implemented to overcome them to help decrease the time between stroke symptom onset and presentation to the ED.

5. Conclusion

Understanding specific patient factors, along with vigilant exploration of system issues, can help prioritize high-risk patients along with guiding the development of potential interventions to enhance timely access, ensure excellent guideline-concordant care, and improve both clinical outcomes and quality of life for patients and their families experiencing stroke burden. Targeting these specific patient populations that experience delayed presentation and identifying specific barriers that influence time of presentation, including lack of medical education, financial considerations, or availability of transportation, is a first step to improving care. Next steps include tailoring interventions that can lead to faster presentation, increasing the number of patients that can qualify for acute treatments, and ultimately improving outcomes in stroke patients.

References

[1] J.L. Saver, G.C. Fonarow, E.E. Smith, et al., Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke, JAMA 309 (2013) 2480–2488.

[2] J.L. Saver, M. Goyal, A. van der Lugt, et al., Time to treatment with endovascular Thrombectomy and outcomes from ischemic stroke: a meta-analysis, JAMA 316 (2016) 1279–1288.

[3] G.W. Albers, M.P. Marks, S. Kemp, et al., Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging, N. Engl. J. Med. 378 (2018) 708–718.

[4] R.G. Nogueira, A.P. Jadhav, D.C. Haussen, et al., Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct, N. Engl. J. Med. 378 (2018) 11–21.

[5] O. Adeoye, R. Hornung, P. Khatri, D. Kleindorfer, Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years, Stroke 42 (2011) 1952–1955.

[6] D.M. Nasr, W. Brinjikji, H.J. Cloft, A.A. Rabinstein, Utilization of intravenous thrombolysis is increasing in the United States, Int. J. Stroke 8 (2013) 681–688.

[7] A.E. Hassan, S.A. Chaudhry, M. Grigoryan, W.G. Tekle, A.I. Qureshi, National trends in utilization and outcomes of endovascular treatment of acute ischemic stroke patients in the mechanical thrombectomy era, Stroke 43 (2012) 3012–3017.

[8] F. Khorvash, F. Heidary, M. Saadatnia, A. Chitsaz, Z. Tolou-Ghamari, Tissue plasminogen activator; identifying major barriers related to intravenous injection in ischemic acute cerebral infraction, J. Res. Med. Sci. 22 (2017) 19.

[9] J.E. Siegler, A.K. Boehme, K.C. Albright, S. Martin-Schild, Ethnic disparities trump other risk factors in determining delay to emergency department arrival in acute ischemic stroke, Ethn. Dis. 23 (2013) 29–34.

[10] M.A. Smith, L.D. Lisabeth, F. Bonikowski, L.B. Morgenstern, The role of ethnicity, sex, and language on delay to hospital arrival for acute ischemic stroke, Stroke 41 (2010) 905–909.

[11] A. Chandratheva, D.S. Lasserson, O.C. Geraghty, P.M. Rothwell, Vascular S. Oxford, Population-based study of behavior immediately after transient ischemic attack and minor stroke in 1000 consecutive patients: lessons for public education, Stroke 41 (2010) 1108–1114.

[12] N. Sprigg, C. Machili, M.E. Otter, A. Wilson, T.G. Robinson, A systematic review of delays in seeking medical attention after transient ischaemic attack, J. Neurol. Neurosurg. Psychiatry 80 (2009) 871–878.

[13] K.G. Smolderen, J.A. Spertus, B.K. Nallamothu, et al., Health care insurance, financial concerns in accessing care, and delays to hospital presentation in acute myocardial infarction, JAMA 303 (2010) 1392–1400.

[14] P. Vilela, Acute stroke differential diagnosis: stroke mimics, Eur. J. Radiol. 96 (2017) 133–144.

[15] American Heart Association, Get With The Guidelines – Stroke [available at, www.heart.org/HEARTORG/Professional/GetWithTheGuidelines/Get-With-The-Guidelines-Stroke_UCM_306098_SubHomePage.jsp, 2020. Accessed March 28, 2018].

[16] L.H. Schwamm, G.C. Fonarow, M.J. Reeves, Get with the guidelines-stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack, Circulation 119 (2009) 107–115.

[17] Center Rural Health Research, Rural-Urban Commuting Area Codes (RUCAs). https://depts.washington.edu/uwruca/, 2020.

[18] S.R. Messe, P. Khatri, M.J. Reeves, et al., Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry, Neurology 87 (2016) 1565–1574.

[19] T.D. Wickens, Multiway Contingency Tables Analysis for the Social Sciences, Erlbaum, Hillsdale, NJ, 1989.

[20] J.P. Tsai, G.W. Albers, Wake-up stroke: current understanding, Top. Magn. Reson. Imaging 26 (2017) 97–102.

[21] G. Thomalla, C.Z. Simonsen, F. Boutitie, et al., MRI-guided thrombolysis for stroke with unknown time of onset, N. Engl. J. Med. 379 (2018) 611–621.

[22] A. Eissa, I. Krass, B.V. Bajorek, Barriers to the utilization of thrombolysis for acute ischaemic stroke, J. Clin. Pharm. Ther. 37 (2012) 399–409.

[23] K.M. Kelly, K.T. Holt, G.M. Neshewat, L.E. Skolarus, Community interventions to increase stroke preparedness and acute stroke treatment rates, Curr. Atheroscler. Rep. 19 (2017) 64.

[24] A. Berglund, K. Schenck-Gustafsson, M. von Euler, Sex differences in the presentation of stroke, Maturitas 99 (2017) 47–50.
[25] R.A. Cree, J. Lynch, M.G. Au, M.F. Myers, Decisions to seek healthcare based on family health history among urban Appalachian women, J. Genet. Couns. 18 (2009) 534–550.
[26] J.R. Finnegan Jr., H. Meischke, J.G. Zapka, et al., Patient delay in seeking care for heart attack symptoms: findings from focus groups conducted in five U.S. regions, Prev. Med. 31 (2000) 205–213.
[27] F. Tudiver, Y. Talbot, Why don't men seek help? Family physicians' perspectives on help-seeking behavior in men, J. Fam. Pract. 48 (1999) 47–52.
[28] N.C.Y. Yeung, Y. Zhang, L. Ji, G. Lu, Q. Lu, Guilt among husband caregivers of Chinese women with breast cancer: the roles of male gender-role norm, caregiving burden and coping processes, Eur. J. Cancer Care (Engl.) 27 (2018) (e12872).
[29] D. Zarhin, Delaying and seeking care for obstructive sleep apnea: the role of gender, family, and morality, Health (London) 22 (2018) 36–53.
[30] T.E. Madsen, K.A. Baird, B. Silver, A. Gjelsvik, Analysis of gender differences in knowledge of stroke warning signs, J. Stroke Cerebrovasc. Dis. 24 (2015) 1540–1547.
[31] M.J. Hall, S. Levant, C.J. DeFrances, Hospitalization for Stroke in U.S. Hospitals, 1989–2009. NCHS Data Brief, No. 95, National Center for Health Statistics, Hyattsville, MD, 2012.