ORIGINAL ARTICLE

Implementation of a wake-up and unknown symptom onset stroke protocol

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ABSTRACT

Background: Establishing a symptom onset timeline for stroke patients is one of the essential aspects of thrombolytic therapy. Implementing an MRI protocol can potentially increase the rate of thrombolytic therapy and expand treatment to patients who would otherwise be excluded.
Objective: This project aimed to increase the rate of thrombolytic therapy by incorporating an additional layer of evaluation within the established acute stroke code process for patients with wake-up stroke (WUS) or unknown symptom onset stroke.
Methods: Patients 18 years of age and older who presented as WUS eligible for thrombolytic therapy underwent acute MRI. Patients with a diffusion weighted image and fluid attenuated inversion recovery mismatch (DWI-FLAIR Mismatch) on MRI were treated with thrombolytic therapy.
Results: Chi-square test of independence showed patients who underwent the MRI protocol (N = 35) had a higher proportion of alteplase (tissue plasminogen activator,tPA) treatment when compared to a similar sample (N = 44) from 2019 acute stoke logs; χ^2 (1, N = 79) = 8.16, p = .006. Six patients received thrombolytic. Safety showed no symptomatic intracerebral hemorrhage (sICH) or deaths.
Conclusions: Results of the project indicated an increased rate of thrombolytic treatment that was statistically significant.

Key Words: Wake-up stroke, Unknown onset, Thrombolysis, Tissue plasminogen activator, Alteplase, Ischemic stroke treatment

1. INTRODUCTION

Experiencing a stroke is a life-altering event that can lead to death or debility. Every 40 seconds, someone in the United States experiences a stroke, and every 3.7 minutes someone dies from a stroke.[1] According to Powers et al.,[2] "cost savings of approximately US $30 million would be realized if the proportion of all ischemic stroke patients receiving thrombolysis was increased to 8%."

Patients treated with alteplase within four and a half hours have an increased likelihood of resolved symptoms or non-disabling symptoms.[3] Only about three to five percent of patients receive treatment with alteplase. Frequently, the patient is unable to provide onset information due to the severity of their deficits. Healthcare providers must rely on family or friends to supply the needed information as symptoms can sometimes start with no one with the patient at the time of onset. In these cases, it is necessary to determine when the patient was last seen normal. A timeline that can be confirmed to be within a four-and-a-half-hour window from the start of symptoms allows the patient to be considered for treatment. However, in 14 to 27% of patients, the onset of

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symptoms is unknown. Many times, this is due to symptom recognition upon awakening from sleep.[4] Currently, patients outside the four-and-a-half-hour window of treatment are excluded from alteplase due to the increased risk of intracranial hemorrhage and the lack of proven benefit. These patients may be left with profound deficits leading to loss of function.

Over the past ten years, there have been several researchers attempting to identify a way to use magnetic resonance imaging (MRI) to determine a timeline for wake-up stroke (WUS) and unknown symptom onset stroke.[4–7] MRI has been determined to be a safe and feasible intervention to determine the timing of symptoms allowing WUS and unknown symptom onset stroke patients to receive thrombolytic treatment with alteplase.[4,7] DWI FLAIR mismatch is the term used to describe the identification of infarcted tissue on diffusion weighted imaging (DWI), with no evidence on T2-weighted fluid-attenuated inversion recovery (FLAIR) suggesting the infarct is within four hours.[8] The DWI-FLAIR mismatch will be used to determine if the patient's acute stroke symptoms are less than or greater than four hours.

Utilizing this advanced imaging modality in the acute phase of stroke quantifies the timing of symptoms to less than four hours, allowing a patient to meet the inclusion criteria for time. If all other inclusion criteria are met, the patient can receive treatment.

Aim of the project

The WUS and Unknown Symptom Onset Stroke project aimed to implement a protocol that focused on stroke patients with unknown symptom onset to increase the rate of treatment with alteplase (tissue plasminogen activator,tPA). The protocol utilized MRI to determine the timing of symptom onset in patients who would otherwise not meet alteplase (tPA) inclusion. The project protocol proposed a 25% increase in the rate of treatment with alteplase (tPA) as compared to previous 0% of patients.

2. METHODS

This was a quality improvement (QI) project that utilized a quasi-experimental nonequivalent group design. Four emergency departments in a major health system in the southern United States participated in the QI project. Project approval was granted through both the health system and university Institutional Review Board (IRB). Subjects were 18 years of age or older and were chosen based on a presentation to the emergency department with stroke or stroke-like symptoms. Patients who had unclear or unknown symptom onset were included. Patients were excluded from participation if symptom onset was known, patients had an obvious exclusion to alteplase (tPA), or in those patients who presented with symptoms suggestive of a large vessel occlusion (LVO).

The WUS and Unknown Symptom Onset Stroke Protocol was added to the existing acute stroke protocol in place at each of the emergency departments, summarized in Figure 1. For patients who presented with WUS and unknown symptom onset and no evidence of large vessel occlusion symptoms, the triage nurse activated a stroke code, identified the patient as WUS, the patient was seen by an emergency department provider and transported for a CT scan to rule out intracerebral hemorrhage and large core infarct. The stroke team was notified of the stroke code and physically came to the emergency department to examine the patient. Inclusion/exclusion for alteplase (tPA) was determined at that time, along with MRI eligibility. The stroke team contacted the MRI technologist for a STAT MRI. The patient was transported to MRI. The Stroke Team provider accompanied the patient to MRI and interpreted the images as they were acquired. If a DWI-FLAIR mismatch was identified, the recommendation for treatment with alteplase (tPA) was discussed with the patient and or family, and verbal consent for treatment was obtained. The alteplase (tPA) order was placed by the Stroke Team provider and administered by the emergency department nurse. The WUS and Unknown Symptom Onset Stroke Protocol are summarized in Figure 2. The WUS and Unknown Symptom Onset Stroke Protocol for community sites is summarized in Figure 3.

Four emergency departments (EDA, B, C, D) in a major health system in the southern United States, which is a tertiary nonprofit, academic hospital and includes a primary and consulting vascular neurology service in-house, capable of responding to stroke codes twenty-four hours a day, seven days a week participated in the QI project. EDA has access to MRI with technologist in-house 24 hours a day, 7 days a week, 365 days a year. EDA is a Joint Commission certified Comprehensive Stroke Center.

The other three participating hospitals are community hospitals and utilize a telemedicine system for vascular neurology coverage. The EDA vascular neurology physicians provide telemedicine consultation via an audio/video system to the community hospitals in collaboration with the emergency department provider and nurse. The system is activated as part of the acute stroke process for any patient presenting with stroke or stroke-like symptoms in the acute phase.

EDB has access to MRI 24 hours a day, 7 days a week, 365 days a year. Technologists are in-house during normal business hours and are on-call after hours, weekends, and holidays. EDC and EDD are not Joint Commission certified centers. They do however, have a well-established stroke

program with a strong acute stroke process. Both hospitals have access to MRI 24 hours a day, 7 days a week, 365 days a year, with technologists available in-house during regular business hours and are on-call after hours, weekends, and holidays.

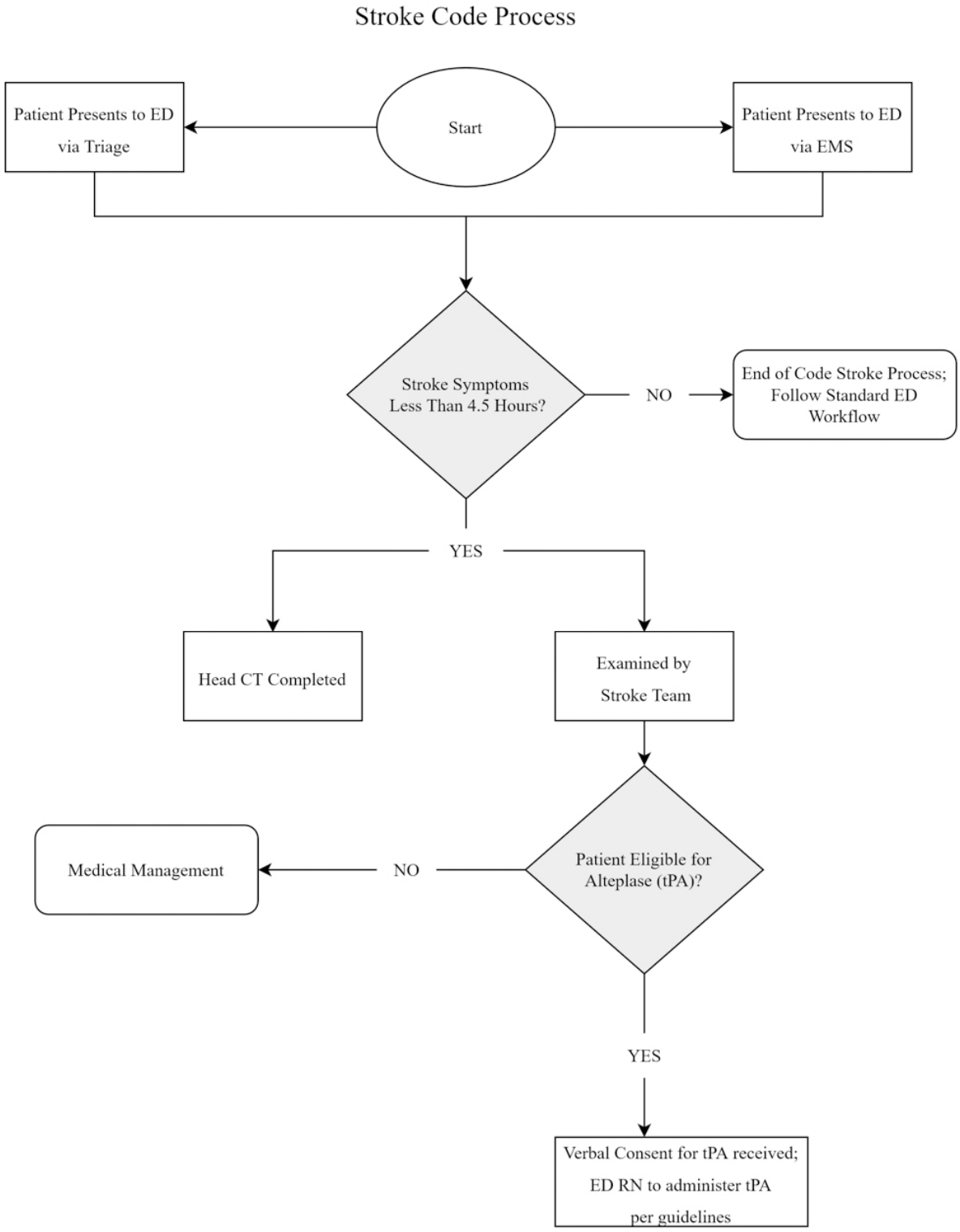

Figure 1. Acute stroke process pre-QI project

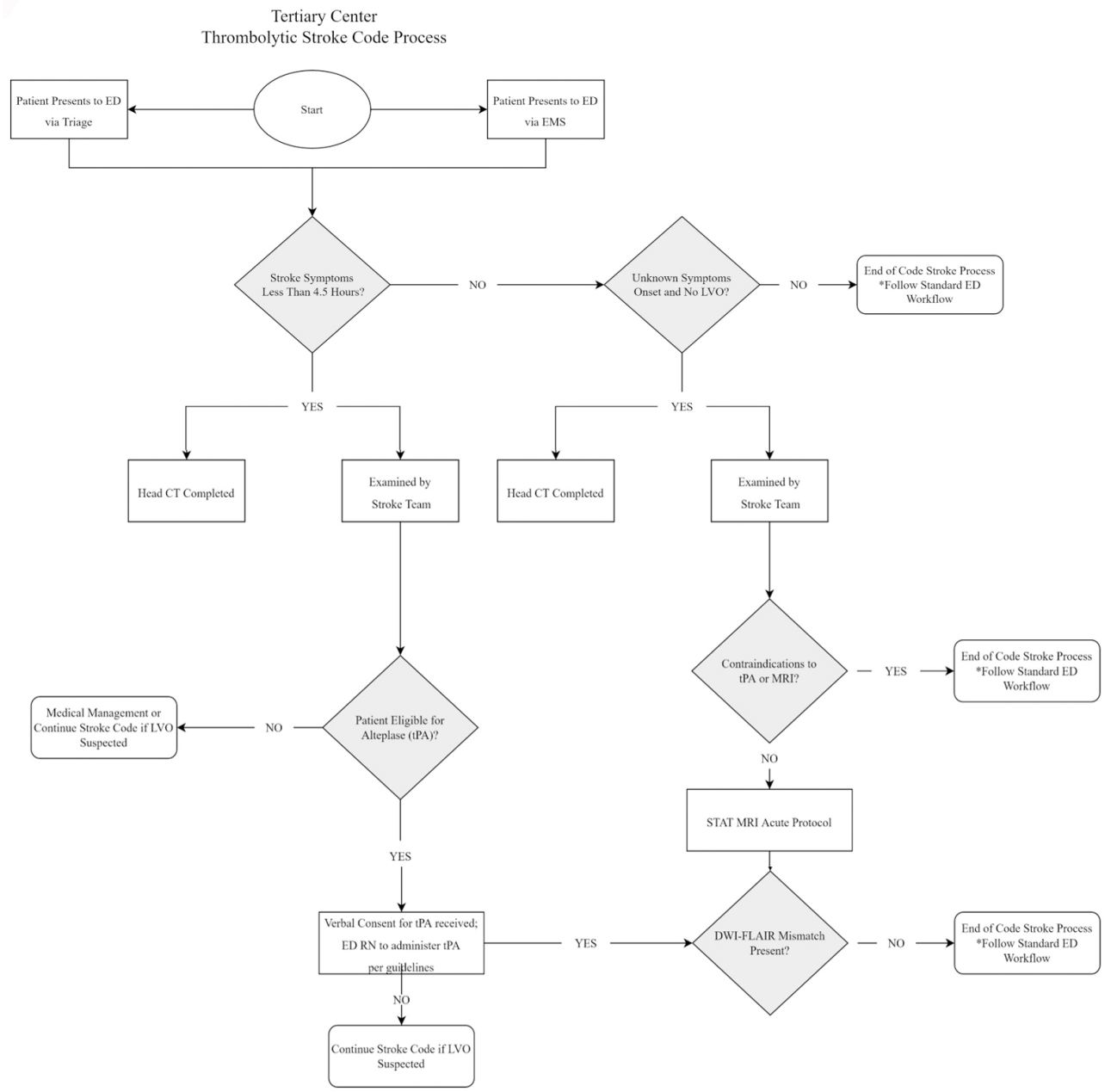

Figure 2. QI project WUS and unknown symptom onset stroke protocol for tertiary center

Table 1. Standard acute stroke process goals for acute stroke care

Acute Stroke Process	Goal
Arrival time to ED provider assessment	10 minutes
Arrival time to stroke team assessment	15 minutes
Arrival time to CT scan completion	20 minutes
Arrival time to CT scan interpretation	45 minutes
Arrival to alteplase (tPA) administration	60 minutes

The primary outcome measured the overall rate of alteplase (tPA) administration. Secondary outcomes included standard acute stroke process goals, shown in Table 1, time from arrival to MRI, arrival to alteplase (tPA) administration, NIHSS at discharge, and Modified Rankin Scale 9Q (mRS-9Q) score at discharge. The NIHSS is a commonly used scale to evaluate the effects of an acute stroke.[6] The mRS-9Q is a widely used tool to evaluate outcomes in research involving stroke recovery and disability.[7]

Demographic data, including age, gender, and ethnicity, were collected. Additional data points around timeliness of alteplase (tPA) were collected and included: last known normal date and time, arrival date and time, triage time, ED

provider time, time stroke code activated, time call placed to RRC, time stroke physician notified, time stroke physician called back, CT order time, CT completion time, CT interpretation time, MRI order time, MRI completion time, MRI interpretation time, time alteplase (tPA) recommended, time alteplase (tPA) ordered, time of alteplase (tPA) bolus, reason alteplase (tPA) not recommended, and reasons for alteplase (tPA) administration delays.

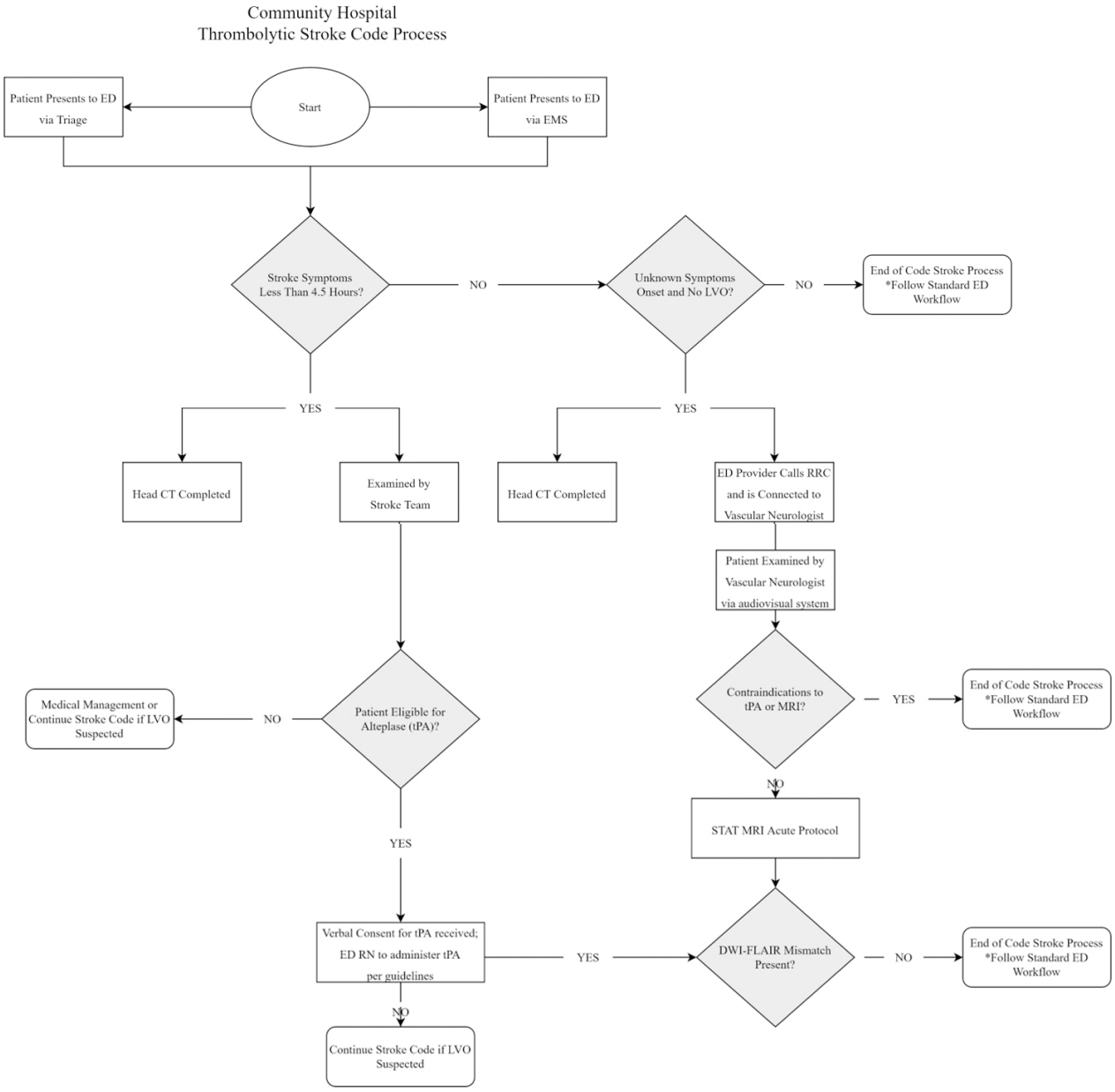

Figure 3. QI project WUS and unknown symptom onset stroke protocol for community hospitals

3. RESULTS

The QI project aimed to improve the rate of thrombolytic therapy for acute stroke patients who awoke with symptoms or who had unknown symptom onset. Data collection began on January 29, 2020 and ended on October 31, 2020. A comparison sample was identified through retrospective chart review during the same period but from the previous 2019 year.

Statistical analysis was performed using IBM SPSS Statistics version 27.0. Descriptive statistics were used to explain the demographic variables. A power analysis for a difference between two independent proportions was conducted in G-POWER to determine the sufficient sample size using an alpha of 0.05, a power of 0.90, and a difference in proportion

of 0.25 indicating a desired sample size of 32 in each group.

A total of 35 patients completed the protocol and were included in the data analysis. The comparison sample was identified using prior data logs from 2019 that captured patients presenting with acute stroke symptoms with 44 patients who meet criteria included in the comparison analysis. The MRI protocol group and the comparison group had similar distributions of all variables with the exception of dyslipidemia (n = 21, 60.0%; n = 16, 36.4%), as seen in Table 2.

Both the initial NIHSS and the discharge NIHSS differed between the two groups. the MRI protocol group had a slightly higher initial NIHSS (M = 6, SD = 6) and a slightly higher discharge NIHSS (M = 5, SD = 5). The discharge mRS-9Q for the MRI protocol group (M = 2, SD = 2) was similar to the comparison group (M = 2, SD = 2), as seen in Table 3.

Table 2. Descriptive statistics for demographic and clinical characteristics of the patients

Variables	WUS/Unknown Symptom Onset Stroke Protocol Group (N = 35)		Comparison Group (No Protocol) (N = 44)	
	n	**%**	***n***	**%**
Gender				
Male	19	54.3	25	56.8
Female	16	45.7	19	43.2
Race				
White	11	31.4	14	31.8
Black	21	60.0	27	61.4
Other	3	8.6	3	6.8
Reason for unknown time of symptom onset				
Nighttime sleep	25	71.4	32	72.7
Daytime sleep	2	5.7	1	2.3
Aphasia, confusion, other	8	22.9	11	25.0
Medical history				
Hypertension	31	88.6	35	79.5
Diabetes mellitus	20	57.1	19	43.2
Dyslipidemia	21	60.0	16	36.4
Carotid disease	2	5.7	1	2.3
Atrial fibrillation	1	2.9	1	2.3
Coronary artery disease	5	14.3	5	11.4
Tobacco abuse	8	22.9	10	22.7
History of ischemic stroke	9	25.7	14	31.8
Received alteplase (tPA)	6	17.1	0	0

Note. WUS = wake-up stroke; tPA = tissue plasminogen activase

Table 3. Additional descriptive statistics

Variable	Received MRI Protocol (N = 35)		Comparison Group (N = 44)	
	M	***SD***	***M***	***SD***
Age	66.1	10.7	66.0	13.7
Initial NIHSS	6	6	4	4
Discharge NIHSS	5	5	3	3
Discharge mRS-9Q	2	2	2	2
Arrival to MRI	1.27	0.42	NA	NA
MRI to tPA Administration	0.25	0.15	NA	NA

Note. NIHSS = National Institute of Health Stroke Scale; mRS-9Q = modified Rankin Score; MRI = magnetic resonance imaging; tPA = tissue plasminogen activase; M = mean; SD = standard deviation; NA = not applicable

Each of the acute stroke process time data points were compared to the standard goal times. There was a significant difference in the arrival to ED provider (M = 0.06, SD = 0.06) compared to the Standard goals (M = 0.10, SD = 0.00); $t(68)$ = -4.31, p = .000, d = -1.05, and arrival to CT interpretation (M = 0.30, SD = 0.22) to Standard goals (M = 0.45, SD = 0.00); $t(68)$ = -3.92, p = .000, d = -0.95. The negative t statistic indicated the Standard goals had longer times in both of these metrics. There was significantly different results seen in arrival to stroke team (M = 0.23, SD = 0.21) as compared to the Standard goals (M = 0.15, SD = 0.00); $t(68)$ = 2.28, p = .026, d = 0.55. The positive t statistic indicated the MRI protocol group had longer times. There was no significant difference when comparing arrival to CT completion (M = 0.24, SD = 0.19) to the Standard goals (**M** = 0.20, SD = 0.00); $t(68)$ = 1.22, p = .227, d = 0.30). Table 4 summarizes this data.

A Mann-Whitney U test indicated there was a difference in the arrival to alteplase (tPA) between those who participated in the WUS and Unknown Symptom Onset Stroke Protocol as compared to standard time goals, suggesting alteplase (tPA) administration was greater for the MRI Protocol group (Mdn = 8.5) than the Standard Goals group (Mdn = 4.5), U = 6, p = .040, r = -0.84, as seen in Table 5.

Mann-Whitney U test indicated there was no difference between time to alteplase (tPA) administration in those participants who received alteplase (tPA) (Mdn = 8.5) as compared to those who did not receive alteplase (tPA) (Mdn = 4.5), U = 60.00, p = .278, r = -0.19, as seen in Table 6.

Table 4. Independent samples t-test results comparing acute stroke processes with standard goals

Outcome	Received MRI Protocol (N = 35)		Standard Goals		$t(68)$	p	d
	M	*SD*	*M*	*SD*			
Time from arrival to ED provider	0.06	0.06	0.10	0.00	-4.31	.000	-1.05
Time from arrival to Stroke team	0.23	0.21	0.15	0.00	2.28	.026	0.55
Time from arrival to CT completion	0.24	0.19	0.20	0.00	1.22	.227	0.30
Time from arrival to CT interpretation	0.30	0.22	0.45	0.00	-3.92	.000	-0.95

Note. M = mean; SD = standard deviation; t = t-test; d = Cohen's d; p = statistical significance; ED = emergency department; CT = computed tomography

Table 5. Mann-Whitney U test comparing acute stroke processes with standard goals

Outcome	Received MRI Protocol (N = 35)		Standard Goals	U	r	p
	M	*SD*	*M*			
Time from arrival to tPA administration	1.22	0.39	1.00	6.00	-0.84	.040

Note. M = mean; SD = standard deviation; p = statistical significance; tPA = tissue plasminogen activase; U = Mann-Whitney; r = effect size; p = statistical significance

Table 6. Mann-Whitney U test comparing time from arrival to Mri for alteplase (tPA) group compared to no alteplase (tPA) group

Outcome	Received tPA (N = 6)		No tPA (N = 29)		U	r	p
	M	*SD*	*M*	*SD*			
Time from arrival to MRI	1.10	0.24	1.41	1.05	60.00	-0.19	.278

Note. M = mean; SD = standard deviation; p = statistical significance; tPA = tissue plasminogen activase; U = Mann-Whitney; r = effect size; p = statistical significance

Table 7. Chi square test of independence results evaluating outcomes between the WUS and unknown symptom onset protocol group with the comparison group

Outcome	WUS/Unknown Symptom Onset Protocol Group (N = 35)		Comparison Group No Protocol (N = 44)		X^2	df	p
	n	%	n	%			
tPA Administration	6	17.1	0	0	8.16	1	.006
sICH	NA	NA	NA	NA	NA	NA	NA
Mortality	NA	NA	NA	NA	NA	NA	NA

Note. WUS = wake-up stroke; X^2 = chi square; df = degrees of freedom; p = statistical significance; tPA = tissue plasminogen activase; sICH = symptomatic intracerebral hemorrhage

Table 8. Independent samples t-test results evaluating outcomes between the WUS and unknown symptom onset protocol group with the comparison group

Outcome	WUS/Unknown Symptom Onset Protocol Group (N = 35)		Comparison Group No Protocol (N = 44)		$t(77)$	p	d
	M	SD	M	SD			
Discharge NIHSS	5	5	3	3	2.33	.023	0.62
Discharge mRS-9Q	2	2	2	2	1.95	.550	0.43

Note. NIHSS = National Institute of Health Stroke Scale; mRS-9Q = modified Rankin Score; WUS = wake-up stroke; M = mean; SD = standard deviation; t = t-test; d = Cohen's d; p = statistical significance

The relationship between the variables, participants who underwent the MRI protocol and received treatment with alteplase (tPA), was significant, $\chi^2(1, N = 79) = 8.16$, $p = .006$. Patients who underwent the MRI protocol had a higher proportion of alteplase (tPA) treatment, as seen in Table 7.

An independent samples t-test for secondary outcomes, as seen in Table 8, found a significant difference in the discharge NIHSS within the MRI protocol group ($M = 5$, $SD = 5$) as compared to the no protocol comparison group ($M = 3$, $SD = 3$); $t(77) = 2.33$, $p = .023$, $d = 0.62$. No significant difference in the discharge mRS-9Q was identified within the MRI protocol group ($M = 2$, $SD = 2$) as compared to the no protocol comparison group ($M = 2$, $SD = 2$); $t(77) = 1.95$, $p = .550$, $d = 0.43$. No participants experienced an sICH or mortality in either group.

4. Discussion

The QI project offered a framework for emergency departments to develop a structured approach to treating WUS and unknown symptom stroke patients. The project provided both statistical significance and clinical significance. A total of 35 patients completed the protocol, with six patients receiving thrombolytic therapy that would historically not have been able to. The impact for those six patients may have ranged from prevention of death to prevention or decreases in the severity of physical and mental limitations, not to mention extreme changes to quality of life that an un-prevented stroke would have caused.

The policy for stroke code activation relied heavily on the nursing staff to activate a stroke code as did the success of implementing a WUS and unknown symptom onset stroke protocol. When comparing the arrival to ED provider in the MRI protocol group to the standard process goals, the ED provider saw the MRI protocol group faster than the standard acute stroke process goal, which was statistically significant ($p = .000$). The finding suggests that nursing's early recognition and stroke code activation prompt the ED provider to examine the patient rapidly. When comparing arrival to Stroke Team evaluation, the MRI protocol group had a longer time as compared to the standard acute stroke process goals, which was also statistically significant ($p = .026$). The finding suggests a possible delay due to a concern of whether consulting the Stroke Team was appropriate and/or a potential need for further education or continued change in culture to early involve the Stroke Team for WUS and unknown symptom onset stroke presentations. Arrival to CT interpretation was well below the standard acute stroke process goal, as seen in Table 1, but patients in the MRI protocol group had a statistically significant longer time to tPA administration ($p = .040$). The results were not surprising, given MRI is not part of the typical acute stroke code evaluation and added an additional layer of evaluation to determine eligibility. Longer times were also seen in Thomalla et al.[5] The mean time between the two groups was not statistically

significant (p = .278), indicating eligibility did not influence how quickly a patient completed the MRI protocol.

Treatment rates with thrombolytic therapy were statistically significantly higher in those patients who completed the MRI protocol (p = .006). There were no symptomatic intracranial hemorrhage (sICH) or mortality associated with the treatment. The safety data are better than what had been presented in the literature supporting the safety of MRI technology to determine eligibility for this population of patients.[4, 7, 9, 11–14]

It is established in the literature that thrombolytic therapy improves outcomes and can be seen with lower NIHSS and mRS-9Q at 90 days within the treatment group.[2, 4, 6, 7, 9, 11–14] There was a statistically significant difference in the discharge NIHSS within the MRI protocol group compared to the no protocol comparison group (p = .023). The finding suggests the MRI protocol group had a higher stroke severity level at discharge than the no protocol comparison group. The noted discharge NIHSS differences between the two groups were also seen in the means for the initial NIHSS, implying the MRI protocol group had an overall higher stroke severity level than the no protocol comparison group even at presentation. No statistically significant difference was seen with the discharge mRS-9Q between the two groups.

A limitation of the project was the differences in MRI availability within each participating site. Only one hospital offered 24/7 coverage and had access to two different MRI scanners. The other sites had varying availability of in-house MRI technologists, and most only had access to one scanner which likely contributed to the longer arrival to MRI completion times. Only one hospital offered 24/7 coverage and had access to two different MRI scanners. The other sites had varying availability of in-house MRI technologists, and most only had access to one scanner. Stroke code patients had to be coordinated between scheduled outpatient MRI appointments. The limitations most likely contributed to some of the longer arrival to MRI completion times. The MRI challenges for one of the selected hospitals led to the inability to implement the project fully. Shortly after training, the hospital only had one MRI technologist, severely limiting their ability to participate. The hospital did not contribute any patients to the project.

An additional limitation to the project was the change in culture needed to create a sense of urgency for MRI imaging. MRI was not a typical imaging modality used in the acute phase of stroke. This limitation may be another contributor to longer arrival to MRI completion times. A final limitation was the challenges of coordinating the MRI completion and notification back to the Stroke Team for timely interpretation in the community hospitals utilizing telemedicine. Not having an electronic process in place limited timely decision-making and may have contributed to longer treatment times.

Recommendations include consistent MRI availability, which is critical for early treatment decisions. The literature demonstrates that stroke is more likely to occur upon awakening and during early morning hours.[15] Extending MRI availability to 5:00 AM, seven days a week could be a viable option to ensure in-house availability. Additionally, an automated notification system for those hospitals that utilize telemedicine would allow for early communication of MRI completion, leading to decreased delays and earlier treatment times.

5. Conclusion

The QI project assessed the implementation of a WUS and unknown symptom onset stroke protocol for adult ischemic stroke patients who presented to the emergency department to determine if the protocol could increase treatment with thrombolytic therapy. Results of the project indicated an increased rate of thrombolytic treatment that was statistically significant. Safety data showed no adverse outcomes associated with the protocol or treatment. The project also demonstrated that the protocol was readily adopted and could be successfully driven by the nursing team.

Conflicts of Interest Disclosure

The authors declare they have no conflicts of interest.

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