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3 **Title:** Predictors of diagnostic neuroimaging delays in adult Ontario patients presenting
4 with symptoms suggestive of acute stroke
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12 **Manuscript type:** original research
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Abstract:

Background: To evaluate factors associated with delay of neuroimaging (computed tomography or magnetic resonance imaging of the brain) in patients with suspected acute stroke.

Methods: Prospective cohort study of all patients older than 18 years with suspected acute stroke seen at hospitals with neuroimaging capacity within the Ontario Stroke Registry between April 1, 2010 and March 31, 2011. We used a hierarchical, multivariable Cox proportional hazards model to evaluate the association between patient and institution factors and the likelihood of receiving neuroimaging within 25 minutes of arrival in the emergency department (ED).

Results: From a cohort of 13,250 patients who presented to an ED with stroke-like symptoms, 3,984 patients arrived within four hours of symptom onset. In these patients neuroimaging was performed within 25 minutes of presentation in 27.3%. The following variables were independently associated with a greater likelihood of neuroimaging completion within 25 minutes of presentation: less time from symptom onset to presentation; more severe stroke; male gender; no past history of stroke or transient ischemic attack (TIA); arrival to hospital from a setting other than home; presentation to a designated stroke centre or an urban hospital.

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3 **Interpretation:** In Ontario, Canada, a minority of patients with stroke-like symptoms
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5 who present within the four-hour thrombolytic treatment window receive timely
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7 neuroimaging. Neuroimaging delays are influenced by an array of patient and hospital
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9 factors, some of which are modifiable.
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Introduction:

Timely access to diagnostic neuroimaging is critical to the management of patients with suspected acute ischemic stroke. Thrombolysis with intravenous tissue plasminogen activator can reduce the risk of disability after stroke, but must be administered within 4.5 hours of stroke onset, and must be preceded by brain imaging to confirm eligibility for thrombolysis.(1) Stroke guidelines developed by the Brain Attack Coalition and the American Heart Association advise the completion of computed tomography (CT) imaging within 25 minutes of arrival to the emergency department,(2-4) while the Canadian Best Practice Recommendations for Stroke Care note that patients with suspected acute stroke or transient ischemic attack (TIA) should receive neuroimaging immediately.(5-9)

Numerous studies have examined the relationship between stroke symptom onset-to-door time and door-to-thrombolysis time (frequently termed “door-to-needle” time).(10-15) However, fewer studies have investigated the door-to-imaging time—one of the first time windows in the management of acute stroke patients—and there is little information on factors associated with delays in brain imaging.(16)

We undertook this study to assess the timing of neuroimaging (CT or magnetic resonance (MR) of the brain) in patients with symptoms suggestive of acute stroke who presented to Ontario hospitals with neuroimaging capacity. We determined the proportion of patients who presented within 4 hours of stroke onset (and thus were

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3 potentially eligible for intravenous thrombolysis) who underwent neuroimaging within 25
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5 minutes of arrival, and identified factors that predicted the likelihood of neuroimaging
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7 within this time.
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10 11 12 13 14 15 **Methods:**

16 17 18 19 ***Data sources:***

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21 The Ontario Stroke Registry (formerly known as the Registry of the Canadian Stroke
22
23 Network (RCSN)) performs a biennial audit of patients with suspected stroke or TIA
24
25 seen in the ED or admitted to hospital at any acute care institution in the province of
26
27 Ontario, Canada, excluding psychiatric hospitals. Chart abstraction is performed by
28
29 specially trained neurology research personnel, and includes abstraction of important
30
31 timing variables including time of stroke onset, time of ED arrival and time of first brain
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33 imaging.(17) We used data from the audit performed in fiscal year 2010/2011 and only
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35 included those hospitals that had neuroimaging capacity, defined as having CT or MRI
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37 on-site.
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45 46 ***Setting:***

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48 Data were collected from Ontario hospitals which were categorized as follows: 1)
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50 regional stroke centre; 2) district stroke centre; and 3) non-designated hospital.
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52 Regional stroke centres are those which use written stroke protocols for emergency
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54 services and within the emergency department ED. Additionally, they can offer CT
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3 neuroimaging, clinicians with stroke expertise and neurosurgical/neurointerventional
4 radiology facilities and have resources similar to those found in American
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6 comprehensive stroke centres. District stroke centres share the features of regional
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8 stroke centres, but do not have onsite neurosurgical/neurointerventional radiology
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10 facilities, and are similar to American primary stroke centres. Non-designated hospitals
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12 are those which do not fit the definition of a regional nor district stroke centre but still
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14 have neuroimaging capability.
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21 22 ***Study population:***

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24 We excluded patients who were less than 18 years of age, had duplicate records, died
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26 prior to receipt of neuroimaging or were transferred from another hospital. We also
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28 excluded patients where the exact time of stroke symptom onset was unknown. In
29
30 order to limit our analyses to patients in whom rapid brain imaging would guide
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32 decisions about eligibility for thrombolysis, we excluded patients who presented to
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34 hospital more than four hours after symptom onset.
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41 42 ***Statistical analysis:***

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44 The characteristics of patients who received and did not receive neuroimaging were
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46 compared using chi-square tests for categorical variables and t-tests for continuous
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48 variables. When the National Institutes of Health Stroke Scale (NIHSS) score was
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50 missing, a formula was used to convert the Canadian Neurological Score to the NIHSS
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52 score.(18) We created a hierarchical Cox proportional hazards model to estimate the
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54 effect of time from presentation to neuroimaging and demographic, medical history,
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3 patient presentation and hospital factors on the receipt of neuroimaging. (See Table 1
4 for a detailed list of these variables.) To account for clustering by hospital type, we
5 performed a random effects, multilevel (two-level) regression analysis with patients
6 being level one units and hospitals level two units in the model. The chi-square test was
7 used for model hypothesis testing. We reported adjusted hazard ratios (AHRs) with 95%
8 confidence intervals. Analyses were performed using SAS statistical software (version
9 9.3, SAS Institute Inc., Cary, NC). P-values less than 0.05 were considered statistically
10 significant and all p-values were based on two-tailed tests.
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27 **Results:**

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31 In 2010/11, 13,250 were enrolled in the Ontario Stroke Registry. After applying the
32 exclusion criteria, our study cohort consisted of 3,984 patients. Of these, neuroimaging
33 was completed within 25 minutes of presentation in 27.3% of patients; 94.0% of these
34 examinations were CT and 6.0% were MR. The greatest proportion of patients who
35 received neuroimaging within 25 minutes were those who presented to the ED within 30
36 to 60 minutes of symptom onset. (Figure 1) The mean time to neuroimaging was 1.49
37 hours (standard deviation, 0.89 hours). On univariate analyses, many factors were
38 associated with receipt of neuroimaging within 25 minutes of presentation in the ED.
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3 On multivariable analysis, patients who were male, who had a greater stroke severity on
4 presentation, who had less time from symptom onset to ED presentation, who had no
5 history of stroke, who arrived at the hospital from a site other than home (e.g., nursing
6 home or continuing care facility), who presented to a hospital that was designated a
7 district or regional stroke centre or was located in an urban setting, were more likely to
8 receive neuroimaging within 25 minutes of presentation to the ED. (Table 2)
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22 Discussion:

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27 Of the 3,984 patients in Ontario who presented to an ED within four hours of symptom
28 onset (i.e. within a time where neuroimaging could have reasonably been performed
29 and the patient would have remained within the 4.5-hour thrombolytic treatment
30 window), neuroimaging was only performed within 25 minutes in 27.3% of patients.
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34 These results suggest that the management of some patients with acute ischemic
35 stroke is suboptimal, and may contributor to otherwise eligible patients not receiving
36 thrombolytic or endovascular therapy.
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46 Few prior studies have examined neuroimaging rates among patients with suspected
47 acute stroke. A study from the United States found that 41.7% of patients with
48 suspected stroke underwent neuroimaging within 25 minutes of hospital arrival;
49 however their study sample was limited to patients who had symptom onset less than or
50 equal to two hours before ED arrival.(19) This reflected the previous recommendation of
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3 a three hour thrombolysis administration window.(19) A number of other studies also
4 examined neuroimaging rates in patients with acute ischemic stroke, or patients who
5 presented with stroke-like symptoms (20-23). However, they restricted their study
6 sample to patients who ultimately received thrombolytic therapy,(20) (21) or estimated
7 rates of imaging within 25 minutes among patients who presented either up to 2.0 or 4.5
8 hours after symptom onset. (19,22,23)
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20 We identified a number of factors that were independently associated with
21 neuroimaging delays. Patients who presented to a rural hospital with imaging capacity
22 were less likely than those presenting to urban hospitals to receive neuroimaging within
23 25 minutes of presentation. This finding is consistent with previous studies suggesting
24 that patients seen at rural centres are less likely to receive neuroimaging (24), use
25 emergency medical services,(25) or be treated with intravenous thrombolysis;(26) and
26 that hospitals with greater volumes of stroke patients have increased rates of
27 neuroimaging.(27) Although we found that patients who presented to designated stroke
28 centers were more likely to receive timely neuroimaging than those seen at other
29 centers, the proportion of patients receiving neuroimaging within 25 minutes was still
30 surprisingly low at 29.1% within regional stroke centres.
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48 Patients who presented with less severe symptoms (based on the NIHSS score on
49 presentation) were more likely than those with more severe stroke symptoms to
50 experience a neuroimaging delay. These findings are consistent with other studies
51 which found that patients with a NIHSS score less than or equal to four had an
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3 increased door-to-needle time,(12) and that patients with more severe stroke at
4 presentation were more likely to receive neuroimaging within 25 minutes.(19) Possible
5 explanations for these findings include a lower diagnostic suspicion for stroke when
6 patient symptoms are milder, or that patients with milder symptoms were deemed not to
7 be candidates for thrombolytic therapy. Patients who had a shorter time from symptom
8 onset to ED presentation received neuroimaging most rapidly. This is in contrast to
9 earlier studies which reported a “neuroimaging paradox”, where patients who presented
10 earlier experienced delayed neuroimaging or time to initiation of thrombolytic
11 therapy.(10,12,15,19,28-30)
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27 We found that women presenting with stroke-like symptoms were less likely to receive
28 timely neuroimaging, which is similar to four other studies, one of which also found a
29 delay in door-to-doctor time(19,31-33). In our study, age and socioeconomic status did
30 not impact neuroimaging time, in contrast to a study conducted in the United States
31 (18). It is possible that Ontario’s universal public coverage of hospital care accounts for
32 this difference.
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43 Our results suggest an urgent need to focus on decreasing neuroimaging time in
44 patients who present with acute stroke in Ontario, in keeping with recent
45 recommendations to shift ischemic stroke policy focus from extending the time window
46 for thrombolytic therapy, to providing more rapid treatment.(34). This should be part of
47 an overall quality improvement initiative such as that suggested by Sauser et al.,
48 wherein neuroimaging time was one of ten evidence-based strategies to increase the
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3 likelihood of timely reperfusion.(20) Recent studies have reported significant
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5 improvement in door-to-imaging performance with the adoption of these
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7 initiatives.(20,35,36) Of note, Ontario has a regional system of stroke care,(37) which
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9 already endorses many interventions designed to facilitate timely reperfusion, including
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11 pre-notification of a suspected stroke by emergency medical services to the receiving
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13 hospital, formation of acute stroke teams, stroke-specific medical order sets, and
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15 encouragement of direct transfer of patients from the emergency department triage area
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17 to the scanner, where possible.
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24 The principle strengths of our study are the large, population-based study sample,
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26 complete and high quality data, statistical analyses accounting for the hierarchical
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28 nature of the data, and the fact that patients were managed after the publication of
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30 recent stroke guidelines.(38) The primary limitation of our study is, as with any
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32 observational study, the potential influence of confounding variables. The OSA did not
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34 collect information about some variables that might impact time to neuroimaging such
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36 as patient preferences, the effect of stroke on the ability to communicate, any advanced
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38 care directives that existed, and emergency department overcrowding.
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46 In summary, we found that only a minority of patients with acute stroke received timely
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48 neuroimaging in Ontario in 2010/2011. There is an urgent need for quality improvement
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50 initiatives to address this issue, as a means of increasing the number of patients with
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52 acute stroke who receive appropriate revascularization therapy.
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Table 1: Characteristics of patients who arrived to an ED within 4 hours of symptom onset and did and did not receive neuroimaging within 25 minutes

Variable	Value	Total (n=3,984)	Timely Neuroimaging (n=1,087)	Delayed Neuroimaging (n=2,897)	P- value
Time from symptom onset to ED presentation (hours)	Mean ± SD	1.49 ± 0.89	1.33 ± 0.75	1.55 ± 0.93	<.001
Time from symptom onset group (hours)	0.0-0.5	280	64 (22.9%)	216 (77.1%)	<.001
	>0.5-1.0	1,245	399 (32.0%)	846 (68.0%)	
	>1.0-1.5	939	273 (29.1%)	666 (70.9%)	
	>1.5-2.0	580	169 (29.1%)	411 (70.9%)	
	>2.0-3.0	585	132 (22.6%)	453 (77.4%)	
	>3.0-4.0	355	50 (14.1%)	305 (85.9%)	
Age group (years)	18-44	149	38 (25.5%)	111 (74.5%)	0.715
	45-64	985	282 (28.6%)	703 (71.4%)	
	65-79	1,446	391 (27.0%)	1,055 (73.0%)	
	>=80	1,404	376 (26.8%)	1,028 (73.2%)	
NIHSS score	NIHSS≤4	2,352	383 (16.3%)	1,969 (83.7%)	<.001
	NIHSS>4	1,348	642 (47.6%)	706 (52.4%)	

	Missing	284	62 (21.8%)	222 (78.2%)	
Gender	Female	1,947	484 (24.9%)	1,463 (75.1%)	<.001
	Male	2,037	603 (29.6%)	1,434 (70.4%)	
Income quintile	1 (lowest)	785	202 (25.7%)	583 (74.3%)	0.830
	2	799	219 (27.4%)	580 (72.6%)	
	3	778	216 (27.8%)	562 (72.2%)	
	4	791	224 (28.3%)	567 (71.7%)	
	5 (highest)	831	226 (27.2%)	605 (72.8%)	
Preferred language	English	3,509	926 (26.4%)	2,583 (73.6%)	0.002
	Other	383	132 (34.5%)	251 (65.5%)	
	UTD	92	29 (31.5%)	63 (68.5%)	
Pre-admission independence	No	1,117	278 (24.9%)	839 (75.1%)	0.034
	Yes	2,867	809 (28.2%)	2,058 (71.8%)	
Past medical history:					
Stroke, TIA, ICH	No	2,789	810 (29.0%)	1,979 (71.0%)	<.001
	Yes	1,195	277 (23.2%)	918 (76.8%)	
Carotid revascularization	No	3,935	1,073 (27.3%)	2,862 (72.7%)	0.839
	Yes	49	14 (28.6%)	35 (71.4%)	
Diabetes mellitus	No	3,084	834 (27.0%)	2,250 (73.0%)	0.527
	Yes	900	253 (28.1%)	647 (71.9%)	

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3	Hypertension	No	1,332	326 (24.5%)	1,006 (75.5%)	0.005
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5		Yes	2,652	761 (28.7%)	1,891 (71.3%)	
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8	Hyperlipidemia	No	2,333	618 (26.5%)	1,715 (73.5%)	0.181
9						
10		Yes	1,651	469 (28.4%)	1,182 (71.6%)	
11						
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13	Dementia	No	3,660	999 (27.3%)	2,661 (72.7%)	0.958
14						
15		Yes	324	88 (27.2%)	236 (72.8%)	
16						
17						
18	Other cardiovascular	No	2,831	732 (25.9%)	2,099 (74.1%)	0.002
19	disease					
20						
21		Yes	1,153	355 (30.8%)	798 (69.2%)	
22						
23						
24	Presentation					
25						
26	characteristics:					
27						
28	Business hours	No	2,552	714 (28.0%)	1,838 (72.0%)	0.189
29						
30		Yes	1,432	373 (26.0%)	1,059 (74.0%)	
31						
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33	Arrived to hospital	Home	3,539	972 (27.5%)	2,567 (72.5%)	0.021
34	from					
35						
36		Nursing, retirement	327	95 (29.1%)	232 (70.9%)	
37						
38		home or complex				
39						
40		continuing care				
41						
42						
43		Other	14	<=5 (35.7%)	9 (64.3%)	
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45						
46		Missing or UTD	104	15 (14.4%)	89 (85.6%)	
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49	Hospital					
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51	characteristics:					
52						
53	Type	Regional stroke centre	1,798	523 (29.1%)	1,275 (70.9%)	<.001
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55		District stroke centre	1,404	521 (37.1%)	883 (62.9%)	
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	Not a stroke centre	782	43 (5.5%)	739 (94.5%)	
Rural hospital	N	3,785	1,081 (28.6%)	2,704 (71.4%)	<.001
	Y	199	6 (3.0%)	193 (97.0%)	
Annual stroke volume	High (>200)	3,341	1,005 (30.1%)	2,336 (69.9%)	<.001
	Medium(101-200)	375	65 (17.3%)	310 (82.7%)	
	Low (0-100)	268	17 (6.3%)	251 (93.7%)	

Legend: SD=standard deviation; IQR=interquartile range; NIHSS=National Institutes of Health Stroke Score; UTD=unable to determine; TIA=transient ischemic attack; ICH=intracranial hemorrhage; <=5: cell value suppressed for reasons of privacy and confidentiality; “rural hospital” is defined as one located in a community with a population < 10,000 persons.

Table 2: Multivariable analysis of receipt of neuroimaging within 25 minutes in patients presenting within 4 hours of stroke symptoms

Variable	Value	Hazard Ratio	HR Lower 95% CI	HR Upper 95% CI	P-value
Time from symptom onset to ED presentation (hours)	<0.5 (ref)	1.00			<0.0001
	0.5-<1.0	1.59	1.21	2.08	
	1.0-<1.5	1.55	1.18	2.05	
	1.5-<2.0	1.37	1.02	1.84	
	2.0-<3.0	1.31	0.96	1.77	
	3.0-4.0	0.81	0.56	1.19	
Age group (years)	>=80 (ref)	1.00			0.40
	18-44	1.13	0.79	1.61	
	45-64	1.16	0.98	1.39	
	65-79	1.06	0.91	1.24	
NIHSS score	NIHSS<=4 (ref)	1.00			<0.0001
	NIHSS>4	3.54	3.09	4.05	
	Missing	2.21	1.61	3.05	
Gender	Male (ref)	1.00			
	Female	0.76	0.67	0.86	<0.0001
Income quintile	1 (lowest) (ref)	1.00			0.43
	2	1.10	0.91	1.34	
	3	1.19	0.97	1.45	
	4	1.15	0.94	1.40	
	5 (highest)	1.18	0.97	1.44	

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3	Preferred language	English (ref)	1.00		0.50
4					
5		Other	1.06	0.86	1.30
6					
7		UTD	0.82	0.55	1.22
8					
9	Pre-admission independence	Yes (ref)	1.00		0.07
10					
11		No	0.85	0.72	1.01
12					
13	Past medical history:				
14					
15	Stroke, TIA, ICH	No (ref)	1.00		<0.001
16					
17		Yes	0.78	0.67	0.89
18					
19	Carotid therapy	No (ref)	1.00		0.13
20					
21		Yes	0.66	0.38	1.13
22					
23	Diabetes mellitus	No (ref)	1.00		0.55
24					
25		Yes	0.96	0.82	1.10
26					
27	Hypertension	No (ref)	1.00		0.18
28					
29		Yes	1.11	0.95	1.28
30					
31	Hyperlipidemia	No (ref)	1.00		0.91
32					
33		Yes	1.01	0.88	1.15
34					
35	Dementia	No (ref)	1.00		0.66
36					
37		Yes	0.95	0.74	1.21
38					
39	Other cardiovascular disease	No (ref)	1.00		0.26
40					
41		Yes	1.08	0.94	1.24
42					
43	Presentation characteristics:				
44					
45	Business hours	Yes (ref)	1.00		0.29
46					
47		No	1.07	0.94	1.22
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49	Arrived to hospital from	Home (ref)	1.00		0.01
50					
51		Nursing, retirement home or	1.21	0.94	1.56
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53		complex continuing care			
54					
55		Other	1.90	0.77	4.67
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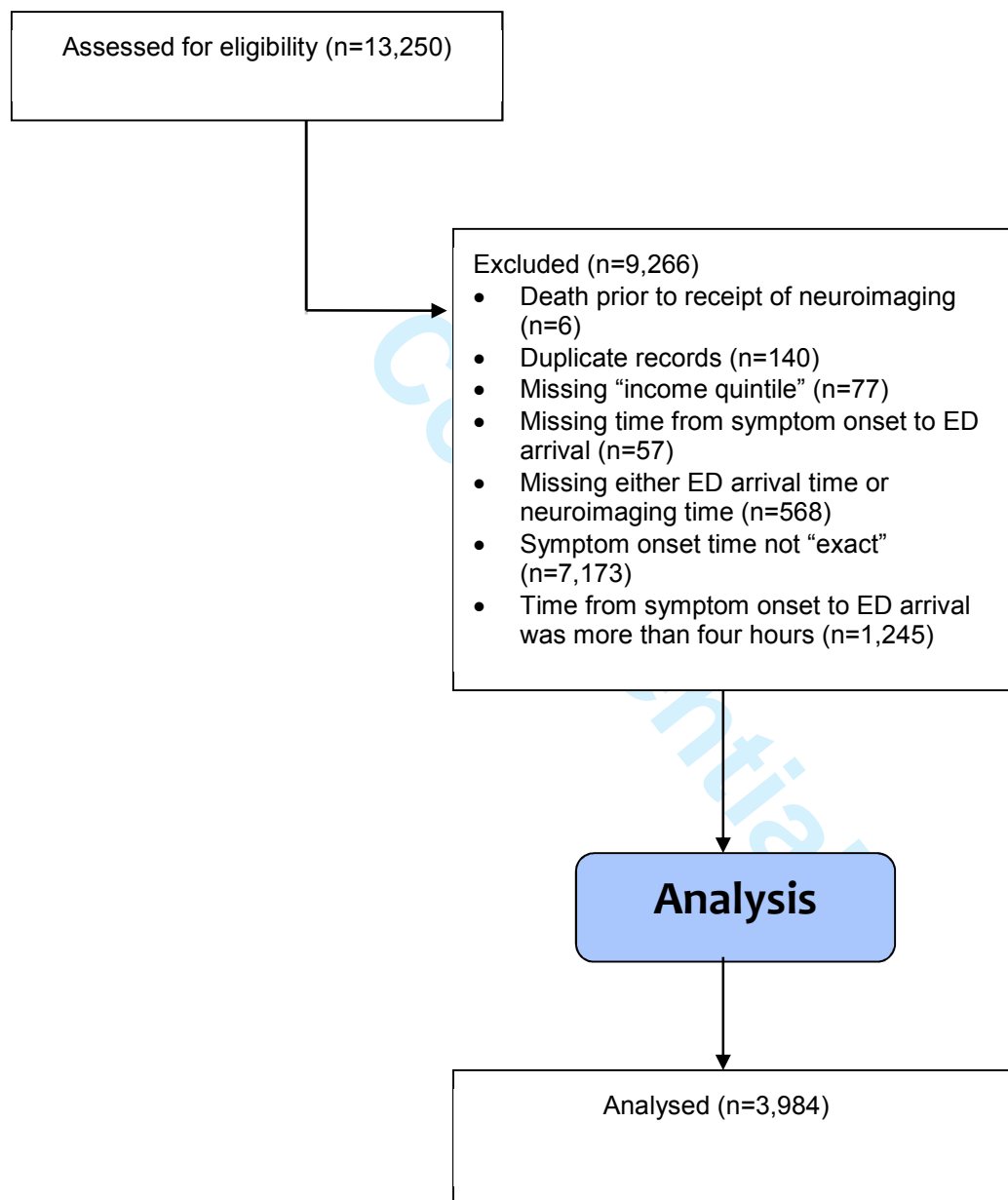
Hospital characteristics:

Type	Not a stroke centre (ref)	1.00			<0.0001
	Regional stroke centre	5.60	2.70	11.62	
	District stroke centre	6.78	3.66	12.56	
Rural hospital	N (ref)	1.00			<0.001
	Y	0.08	0.02	0.36	
Annual stroke volume	High (>200) (ref)	1.00			0.14
	Medium (101-200)	1.06	0.54	2.05	
	Low (0-100)	2.73	1.00	7.47	

Legend: HR=hazard ratio; CL=confidence limit; ref=reference; NIHSS=National Institutes of Health Stroke Score; UTD=unable to determine; TIA=transient ischemic attack; ICH=intracranial hemorrhage.

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Appendix A: Flow diagram for patient cohort*



* Cohort inclusion criteria: adult patients with stroke-like symptoms who presented to a hospital with neuroimaging capacity within four hours of symptom onset and whose time from symptom onset to presentation was exactly known.

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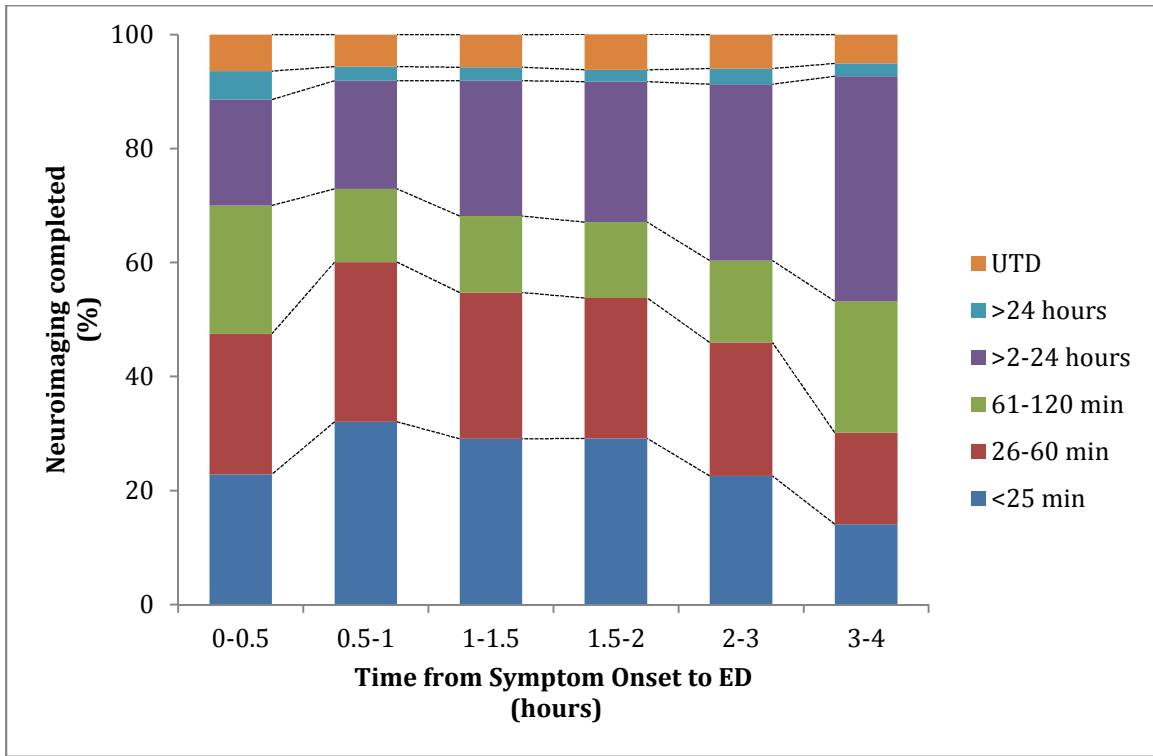
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Figure 1: Time categories within which neuroimaging was completed vs. time from symptom onset to ED arrival



Legend: ED = emergency department; UTD = unable to determine.