Original Article



Extended Delays in Recognition of Stroke Symptoms and Stroke Code Activation for In-Hospital Strokes: The DELAY Study

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ABSTRACT: *Background:* Patients with stroke while hospitalized experience important delays in symptom recognition. This study aims to describe the overall management of an in-hospital stroke population and how it compares with an out-of-hospital community-onset stroke population. *Methods:* In this retrospective observational study, we included consecutive patients with in-hospital and out-of-hospital strokes (both ischemic and hemorrhagic) over a period of one year treated at a comprehensive stroke center. Demographic and clinical data were extracted, and patient groups were compared with regard to stroke treatment time metrics. *Results:* A total of 362 patients diagnosed with acute stroke were included, of whom 38 (10.5%) had in-hospital and 324 (89.5%) had out-of-hospital strokes. The median delay to stroke recognition (time between the last time seen well and first time seen symptomatic) was significantly longer in in-hospital out-of-hospital strokes (77.5 [0–334.8] vs. 0 [0–138.5] min, *p* = 0.04). The median time interval from stroke code activation to the arrival of the stroke team at the bedside was significantly shorter in in-hospital versus out-of-hospital cases (10 [6–15] vs. 15 [8–24.8] min, *p* = 0.01). In-hospital strokes were less likely to receive thrombolysis (12.8% vs. 45.4%, *p* < 0.01) with significantly higher mortality (18.2% versus 2.6%, *p* < 0.01) and longer overall median hospital strok symptom recognition and stroke code activation for in-hospital stroke patients despite comparable overall stroke time metrics. Development of in-hospital stroke symptom recognition should be implemented to improve care for hospital stroke symptom recognition should be implemented to improve care for hospital stroke patients.

RÉSUMÉ : Délais prolongés de la reconnaissance des symptômes d'un AVC et de l'activation d'un code de l'AVC pour des attaques cérébrales survenues en milieu hospitalier : l'étude DELAY. Contexte : Les patients victimes d'un AVC en cours d'hospitalisation subissent d'importants retards dans la reconnaissance de leurs symptômes. Cette étude vise ainsi à décrire la prise en charge globale d'un groupe de patients victimes d'un AVC tout en étant hospitalisés et à la comparer à celle d'un groupe de patients victimes d'un AVC survenu en dehors du milieu hospitalier. Méthodes: Dans cette étude observationnelle rétrospective, nous avons inclus une série de patients consécutifs victimes d'un AVC à l'hôpital ou en dehors d'un hôpital (ischémique ou hémorragique), et ce, pendant une période d'un an. À noter que tous ces patients ont été traités dans un centre spécialisé des AVC. Dans un premier temps, des données démographiques et cliniques ont été extraites ; ensuite, les groupes de patients ont été comparés entre eux en ce qui concerne les temps de traitement de leur AVC. Résultats : Au total, 362 patients ayant reçu un diagnostic d'AVC aigu ont été inclus, dont 38 (10,5 %) victimes d'un AVC en milieu hospitalier et 324 (89,5 %) en milieu extrahospitalier. Le délai médian de reconnaissance des AVC, à savoir le temps écoulé entre la dernière fois qu'un patient s'était senti bien et la première fois qu'on a noté ses symptômes, était notablement plus long dans le cas des AVC survenus en milieu hospitalier que dans celui des AVC survenus en milieu extrahospitalier [77,5 minutes (0-334,8) contre 0 minute (0-138,5); p = 0,04]. Le délai médian entre l'activation d'un code de l'AVC et l'arrivée d'une équipe de l'AVC au chevet d'un patient était significativement plus court dans les cas intra-hospitaliers que dans les cas extrahospitaliers [10 minutes (6-15) contre 15 minutes (8-24,8); p = 0,01]. Outre une mortalité significativement plus élevée (18,2 % contre 2,6 %; p = 0,01) et une durée médiane d'hospitalisation plus longue [3 jours (1-7) contre 12 jours (7-23); p < 0,01], ajoutons que les cas intra-hospitaliers étaient moins susceptibles de recevoir une thrombolyse (12,8 % contre 45,4 %; p = 0,01). *Conclusion* : Cette étude a donné à voir des retards notables dans la reconnaissance des symptômes de l'AVC et l'activation d'un code de l'AVC pour les patients victimes d'une attaque cérébrale en cours d'hospitalisation, et ce, malgré une trajectoire générale d'intervention comparable en ce qui regarde une telle attaque. L'élaboration de protocoles de prise en charge des AVC en milieu hospitalier et la formation systématique du personnel à la reconnaissance des symptômes de l'AVC devraient en conséquence être mises en œuvre pour améliorer les soins prodigués aux patients hospitalisés.

Keywords: hemorrhagic stroke; in-hospital stroke; ischemic stroke; quality improvement; thrombectomy; thrombolysis

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In-hospital strokes account for approximately 6.5% to 15% of all strokes but are associated with higher mortality, extended hospitalization and less rehabilitation potential.¹⁻³ Patients who suffer an stroke while being hospitalized often have many comorbidities, including thromboembolic risk factors.^{1,4,5} Medical procedures and surgery also confer a higher risk of stroke.⁶ Management of strokes during hospital stay is challenging as many confounding factors such as delirium, immobilization or sedation may contribute to delays in the recognition of stroke symptoms. Comorbid conditions, functional status and postsurgical bleeding risks can limit eligibility for thrombolysis. Compared to out-of-hospital strokes, strokes in hospitalized patients are associated with a less guideline-based stroke treatment from the medical team.³ Intracerebral hemorrhage (ICH) can also occur inhospital and is associated with higher mortality than ischemic stroke.7 While patients with ICH cannot benefit from acute reperfusion therapies, rapidly lowering blood pressure, reversing anticoagulation, controlling blood sugar levels and treating fever can improve functional outcomes, and these patients should also be managed urgently.⁸⁻¹⁰ Delays in diagnosis and treatment should be shortened as much as possible to optimize patient outcomes.

The **Diagnosis and EvaLuation of stroke in-hospitAl and in the communitY (DELAY)** study aims to describe the in-hospital stroke population at a single comprehensive stroke center and compare their baseline characteristics, time metrics and treatment with out-of-hospital stroke patients to identify areas for possible improvement.

Methods

We conducted a single-center, retrospective cohort study of all acute ischemic or hemorrhagic strokes that occurred between November 27, 2017, and November 27, 2018, at a large academic comprehensive stroke center in Montreal, Canada. Patient data were retrieved by hospital chart review by medical archivists using ICD codes including cases with stroke as a final diagnosis or as a complication of hospitalization. In addition, cases were identified by a review of the electronic patient record, which includes data from all acute stroke codes evaluated by the vascular neurology team – the MOntreal Neurovascular and StrokE data Repository (MONSTER).

We excluded patients with subacute out-of-hospital strokes (patients with a delay of more than 24 hours from last seen well to first seen symptomatic), stroke mimics and transient ischemic attack and patients who were initially evaluated in another center and transferred for thrombectomy. After a review of imaging reports, patients in whom the acute stroke was an incidental finding were excluded.

Patient characteristics

Baseline patient characteristics including the type of stroke (hemorrhagic or ischemic) and prior use of antithrombotic treatment were documented. Medical or surgical procedures in the days preceding the stroke were recorded.

Stroke time metrics

We used a standardized data collection form in all acute stroke cases assessed by the neurovascular team. The time of imaging was calculated using the time recorded at the start of acute neurovascular imaging. The time of thrombolysis was defined as the time of administration of an intravenous (IV) bolus of thrombolysis. The time of thrombectomy was defined as the time of initial arterial puncture in the angiography suite.

Statistical analysis

We summarized baseline characteristics using descriptive statistics such as median and interquartile ranges (IQR) or frequencies (proportions) where appropriate. We performed univariable comparisons of the median time intervals from the last time seen well to first time seen symptomatic, stroke code activation, stroke team arrival at bedside, imaging and treatment initiation (thrombolysis, thrombectomy) using either the chi-square test or Fischer exact test (with expected cell frequencies less than 5) for nominal data and the Mann–Whitney U test for ordinal data with a cutoff for statistical significance of 0.05. The analyses were performed using Statistical Package for Social Sciences (SPSS) version 27 (Armonk, NY).

Results

A total of 362 patients were diagnosed with an acute stroke during the study period. Thirty-eight patients (10.5%) had strokes inhospital, while 324 (89.5%) had out-of-hospital strokes as seen in Figure 1. The demographic features and comorbidities of each group are presented in Table 1. Both groups were comparable in terms of conventional cerebrovascular risk factors except for a higher prevalence of history of cancer in the in-hospital group (p = 0.02). Anticoagulation was stopped for a medical procedure in significantly more in-hospital patients as compared to the out-ofhospital treatment group. Among the 38 in-hospital patients, 23 underwent a procedure shortly before their stroke (60.5%) (Table 2).

Among the 324 out-of-hospital patients, 74% were assessed by the stroke team within 4.5 hours of the last time seen well compared to 57% in the in-hospital group (p = 0.03). In the out-ofhospital group, 45.4% received thrombolysis compared to 12.8% in the in-hospital group (p = 0.02). In terms of stroke time metrics as shown in Table 2, the median delay to stroke onset recognition (time between the last time seen well and first time seen symptomatic) was 77.5 (0-334.8) min in hospitalized patients and 0 (0–138.5) min in out-of-hospital patients (p = 0.04), presumably because more out-of-hospital strokes were witnessed at the onset. After stroke recognition, the time to stroke code activation was similar for in-hospital and out-of-hospital cases (60 [25-141] vs. 58 [37-107.8] min, p = 0.72). On the other hand, the median time interval from stroke code activation to the arrival of the stroke team at the bedside of the patient was significantly shorter in hospitalized patients compared to out-of-hospital patients (10 [8-15] vs. 15 [8-24.8] min, p = 0.01). Time to imaging and treatment initiation including thrombolysis and thrombectomy were similar between groups. Out-of-hospital patients were significantly more likely to receive thrombolysis (45.4% vs. 12.8%, p < 0.01), whereas thrombectomy rates were not statistically different in both groups (24.4% vs. 12.8%, p = 0.12).

The proportion of patients with ICH was similar in both the in-hospital and out-of-hospital groups (10.5% and 10.8%). Among in-hospital patients with ICH, three of four (75%) had a recent procedure (nephrectomy, carotid endarterectomy and mitral valve replacement). Regarding acute ICH management of hospitalized patients, two out of four (50%) received IV blood pressure-lowering therapy (one before and one after the arrival of the stroke team), while 2 out of 4 (50%) did not need any change in their medication. All four hospitalized patients with ICH died during hospitalization. For out-of-hospital patients with ICH, only 4 out

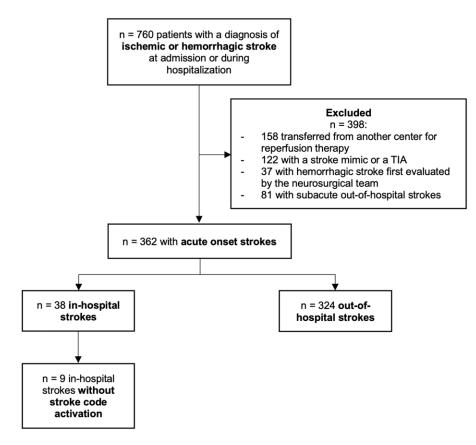


Figure 1. Flow chart of patient selection for the DELAY study.

of 35 (11%) patients did not receive any IV blood pressurelowering therapy, and 10 (29%) died while hospitalized.

Patients with in-hospital stroke included those with and without varied invasive procedures prior to the incident stroke (Table 3 and Table 4). The code stroke was not called for nine in-hospital stroke patients (23.7%) and specific reasons could not be identified on a retrospective review of the case records. In-hospital patients had significantly higher mortality (12.0% vs. 36.0%, p < 0.01) and longer overall median hospital stay (3 [1–7] vs 12 [7–23] days, p < 0.01) than out-of-hospital patients.

Discussion

In this observational, retrospective cohort study comparing inhospital and out-of-hospital patients at our comprehensive stroke center, we found significantly longer delays for stroke symptom recognition in hospitalized patients with similar time intervals to stroke code activation in both groups. There were no statistically significant differences in the overall management times after activation of the stroke team.

Stroke recognition delays

A possible explanation for the significantly longer delay in stroke symptom recognition in hospitalized versus out-of-hospital cases is that most patients in the community recognized their symptoms immediately by themselves or had witnessed stroke onset with rapid emergency medical service activation by bystanders. Contrarily, hospitalized patients may be less alert or have other conditions masking their stroke symptoms and may have the onset of a stroke while unsupervised in their room. We can infer that valuable time is lost in hospitalized stroke patients due to delays in the recognition of stroke symptoms. It is also important to acknowledge that there may be patients with out-of-hospital strokes who may not have been appropriately referred to the stroke team irrespective of stroke code activation.

A delay in timely stroke recognition among in-hospital patients has been found in several other studies.¹¹⁻¹³ Akbik et al. (2020) determined that fewer than 30% of patients were assessed within 90 min, and more than 25% were not seen within 12 hours of symptom recognition.¹¹ In-hospital stroke patients may be subject to significantly longer delays from onset to imaging and from imaging to treatment.¹² A large Canadian cohort comparing stroke care delivery and outcome for 973 patients with in-hospital strokes and 28 837 patients with out-of-hospital strokes revealed significantly longer times in symptom recognition among in-hospital patients, with a smaller proportion undergoing brain imaging.¹³

Several hypotheses could help explain these findings. First, public awareness campaigns have been focused on FAST signs and symptoms recognition in the community¹⁴, but the same efforts have not been devoted to training hospital personnel for acute stroke detection.¹⁵ Delays in stroke code activation for hospitalized patients may also stem from infrequent patient evaluations by staff, particularly among patients considered stable, and the absence of families or caregivers at the bedside. Second, many symptoms can be misattributed to another comorbid condition. For example, speech disturbance, drowsiness or dizziness can be erroneously associated with medication use, a postsurgical state or delirium.^{1,16} Paresis can also go unnoticed in a bedridden patient if there is no standardized screening for neurological deficits by clinical staff.

Stroke code activation

We observed similar time intervals to stroke code activation in hospitalized and out-of-hospital stroke patients even though this

Table 1. Baseline characteristics of out-of-hospital and in-hospital stroke patients

Characteristics of stroke patients	Out-of-hospital n = 324 (89.3%)	In-hospital n = 38 (10.5%)	<i>p</i> -value
Male (%)	157 (48.5%)	18 (47.4%)	0.99
Median age, years (IQR)	76 (63–85)	71.5 (66–80)	0.20
Intracerebral hemorrhage (%)	35 (10.8%)	4 (10.5%)	1.00
Medical history			
Previous stroke	61 (18.8%)	9 (23.7%)	0.47
Previous cardiovascular event	60 (18.5%)	11 (29%)	0.13
Atrial fibrillation	63 (19.4%)	5 (13.2%)	0.37
Hypertension	220 (67.9%)	27 (71.1%)	0.67
Dyslipidemia	153 (47.2%)	21 (55.3%)	0.50
Diabetes mellitus	93 (28.7%)	12 (31.6%)	0.68
Smoker	75 (23.1%)	6 (15.8%)	0.17
Cancer	33 (10.2%)	9 (23.7%)	0.02
Baseline medications			
Antiplatelet agent	108 (33.3%)	18 (47.4%)	0.09
Anticoagulant	37 (11.4%)	4 (10.5%)	1.00
Anticoagulant and antiplatelet agent	10 (3.1%)	4 (10.5%)	0.05
Anticoagulation stopped pre-procedure	7(2.2%)	5(13.2%)	<0.01
Treatment			
Intravenous thrombolysis	147 (45.4%)	5 (12.8%)	<0.01
EVT	79 (24.4%)	5 (12.8%)	0.12
Intravenous thrombolysis and EVT	59 (18.2%)	1 (2.6%)	0.02
Stroke team evaluation within 4.5 hours of LSW	240 (74%)	16 (57%)	0.03
Outcomes			
Duration of hospital stay (median days, IQR)	3 (1–7)	12 (7–23)	<0.01
Death	39 (12.0%)	14 (36.8%)	<0.01
Discharge home	56 (17.3%)	5(13.2%)	0.52

EVT = endovascular thrombectomy; IQR = interquartile range; LSW = last seen well.

Table 2. Time metrics for out-of-hospital and in-hospital stroke patients

Time metrics in minutes (median, IQR) of stroke patients	Out-of-hospital (<i>n</i> = 324)	In-hospital (<i>n</i> = 29 out of 38)	<i>p</i> -value
LSW to first seen symptomatic	0 (0-138.5)	77.5 (0–334.8)	0.04
First seen symptomatic to stroke code activation	58 (37–107.8)	60 (25–141)	0.72
Stroke code activation to stroke team arrival at bedside	15 (8–24.8)	10 (6–15)	0.01
First seen symptomatic to stroke team arrival at bedside	75 (55.3–124.5)	70 (35–147.5)	0.38
Stroke team arrival at bedside to imaging	11 (7–16)	9 (-6.5-24.8)	0.38
First seen symptomatic to imaging	88 (65–135)	82.5 (45–138.3)	0.14
Stroke team arrival at bedside to thrombolysis	23 (17–33) (<i>n</i> = 147)	36 (22–81) (<i>n</i> = 5)	0.13
First seen symptomatic to thrombolysis	99.5 (76.8–139.3) (<i>n</i> = 147)	56 (49.5–116) (<i>n</i> = 5)	0.07
Stroke team arrival at bedside to EVT	51 (39–63) (<i>n</i> = 79)	40 (26.5–79.5) (<i>n</i> = 5)	0.65
First seen symptomatic to EVT	118 (100–160) (<i>n</i> = 79)	109 (59–157.5) (<i>n</i> = 5)	0.39

IQR = interquartile range; LSW = last seen well, EVT = endovascular thrombectomy.

delay should presumably be shorter given that they are surrounded by healthcare staff. It is also concerning that the stroke team was not notified for 9 of the 38 in-hospital stroke patients (23.7%), thereby limiting their access to acute reperfusion therapy. A possible explanation may be that seven out of nine patients had recent surgery (77.8%), which may have been deemed an

Table 3. In-hospital stroke patients with procedures prior to stroke (n = 23 out of 38)

Service of hospitalization	n
Cardiothoracic surgery	
Coronary artery bypass	3
Mitral valve replacement	1
Aortic valve replacement	2
Aortic valve replacement with coronary artery bypass	1
Coronary artery bypass with carotid endarterectomy	1
Cardiopulmonary surgery	
Pulmonary lobectomy	1
Cardiology	
Coronary angiography with angioplasty	1
Diagnostic coronary angiography	2
Gynecology	
Hysterectomy	1
Vascular surgery	
Carotid endarterectomy	1
Thoracic endovascular aortic repair	1
Urology	
Nephrectomy	1
Neurosurgery	
Spinal fixation (laminectomy with discectomy)	1
Endoscopic clivus chordoma removal	1
Interventional neuroradiology	
Diagnostic cerebral angiography	1
Anterior communicating artery aneurysm coiling	1
Orthopedics	
Total hip replacement	1
Hepatobiliary surgery	
Hepatectomy	1
Endoscopic biliary drainage	1

automatic contra-indication to thrombolysis by the treating medical team – but in which case urgent neurovascular evaluation would still be indicated, to consider patient eligibility for endovascular thrombectomy.

Others have also reported delayed stroke team activation even after the recognition of a possible stroke by medical staff in hospitalized patients,¹² which may in part be due to the absence of clear protocols and care pathways for these patients. If bedside staff notify the treating physician or on-call resident instead of directly activating the stroke code, delayed notification is assured. Another possible reason for delay could be erroneous attribution of stroke symptoms to non-acute neurological symptoms triggering delayed general neurology consultations instead of direct stroke team activation.¹ Furthermore, patient comorbidities and their postsurgical state may bias staff towards prematurely concluding that stroke activation is futile or of little benefit. This only underscores the importance of widespread education regarding the availability **Table 4.** In-hospital stroke patients without procedures prior to stroke (n = 15 out of 38)

Service of hospitalization	n
Cardiology	3
Hepatobiliary surgery	2
Hematology	2
Cardiac surgery	1
Digestive surgery	1
Obstetrics	1
Geriatrics	1
Internal medicine	1
Nephrology	1
Stroke neurology	1
Unspecified	1

of effective non-thrombolytic treatment options like mechanical thrombectomy, even in later time windows, which can reduce post-stroke morbidity and mortality.

Stroke investigation and treatment

Streamlined workflows with rapid access to baseline neurovascular imaging are essential in effective acute stroke management. In our study, the median time from "first time seen symptomatic" to imaging was not significantly different between in-hospital and out-of-hospital stroke groups. However, this represents suboptimal management of hospitalized strokes as these patients are already physically closer to the imaging suite. Given the very short delays between imaging and treatment initiation (i.e. time to administration of a bolus of IV thrombolysis) in both groups (9 min in hospitalized and 11 min in out-of-hospital strokes), our results emphasize that time from symptom onset to imaging is where quality improvement efforts should be focused for in-hospital strokes. Again, formal protocols detailing where neurovascular imaging should be done for in-hospital strokes (e.g., emergency department CT vs. radiology department CT) and where thrombolysis administration should occur (e.g., CT scan room, stroke unit, ICU, patient's own unit) can better inform hospital personnel and thereby reduce uncertainty and unnecessary delays.

Only 57% of in-hospital patients were evaluated by the stroke team within 4.5 hours of the last time seen well as compared to 74% of out-of-hospital patients (p = 0.03). The significant discrepancy (p = 0.01) between the proportion of patients who received thrombolysis in strokes in hospitalized patients (12.8%) and out-of-hospital strokes (45.4%) is likely only partially explained by delayed evaluations. We found a similar discrepancy between patients who had both thrombolysis and thrombectomy being 2.6% in the in-hospital group and 18.2% in the out-of-hospital (18.2%), (p = 0.02) stroke group. Given that 62.8% of hospitalized stroke patients had a recent procedure or surgery prior to their stroke, IV thrombolysis is more likely to be contraindicated in this group. The difference in thrombolysis administration rates was not explained by anticoagulant use, as the proportion of anticoagulated patients was similar in both groups.

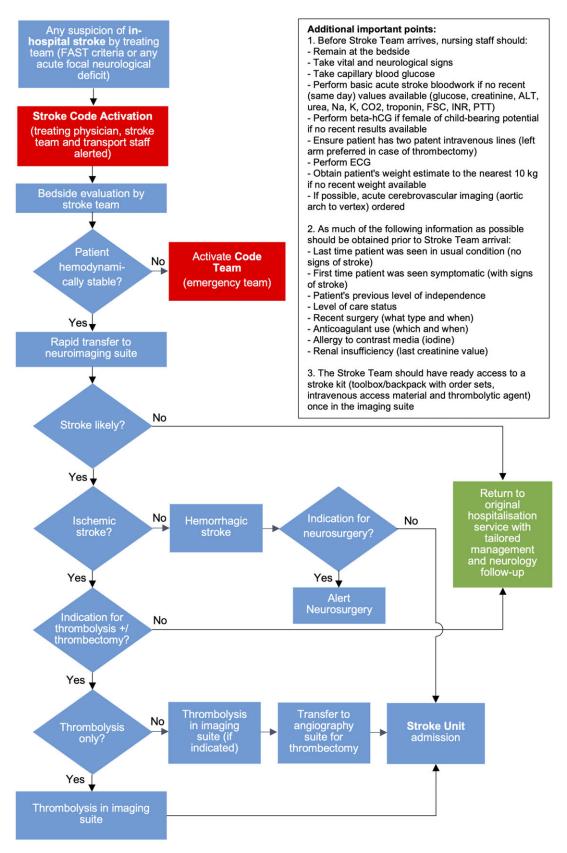


Figure 2. Proposed in-hopital stroke management algorithm.

Potential solutions

The management of in-hospital strokes could, in theory, be more rapid and streamlined, given that the patient is already hospitalized and monitored by medical personnel. There is certainly an unmet need for stroke awareness education among medical and nonmedical staff. Recognition of sudden-onset focal neurological deficits using simple tools like FAST, as well as regular training to identify other stroke-like symptoms among patients with preexisting comorbidities, should be offered to all clinical hospital staff caring for in-patients. Training should also focus on nursing or medical staff notifying the stroke team using the stroke code as soon as there is a suspicion of stroke, without notifying the general neurology team or general on-call resident first. The development of an in-hospital stroke protocol can increase the efficiency of patient management and treatment administration (see the algorithm detailing the standard of care for the treatment of in-hospital strokes at our center in Figure 2).24 Indeed, having clear directions to follow makes it easier for healthcare professionals to react within the therapeutic time window, thereby reducing management delays and increasing the possibility for inhospital stroke patients to have access to appropriate acute stroke treatment.^{16,25-27} These need to be tailored to local infrastructure but should include clear delineation of the medical team responsible for patient evaluation (stroke physician, stroke nurse), having rapid access to thrombolytic therapy (e.g., a dedicated stroke toolbox for in-hospital strokes in a fixed, easily accessible location), ensuring proper IV access and acute stroke laboratory tests, identifying patient transport protocols and location of neurovascular imaging, determining where thrombolytic therapy will be administered and where the patient will be admitted for specialized stroke care. Implementation of regular stroke code activation simulations following detailed in-hospital protocols may also contribute toward reducing false-positive activations, which can represent an important burden on acute neurology services.

Strengths

A strength of this study is the inclusion of patients for whom the stroke team was not notified, comparing patients identified by the medical archivists using ICD codes with data from the electronic patient record that includes all acute stroke codes evaluated by the vascular neurology team. Given that a large majority of these "missed" patients were postoperative, we identified an area of unmet need wherein future quality improvement initiatives could be tailored to focus on surgical and intensive care units. Another strength was the use of standardized data collection tool among patients for whom the stroke team was activated, using a clinical report form completed at the time of patient evaluation, allowing for more complete retrospective data gathering.

Limitations

Our study has several limitations. The retrospective design is subject to many pitfalls and biases. Our sample size was relatively small and captured from a single comprehensive stroke center, with insufficient power to provide statistical significance when comparing both groups and attenuating generalizability of our findings. Our results were heterogeneous, representing the diversity of stroke cases encountered but also limiting the analysis and without adjustment for potential confounding factors. The calculation of stroke metrics like time to imaging could be influenced by variability in estimation of first onset of stroke symptoms in both groups. Our study did not evaluate patients with false-positive stroke code activations. Finally, we did not have access to clinical outcomes beyond the index hospitalization period.

Conclusion

This study did not reveal significant differences between overall treatment time metrics in the management of in-hospital compared to out-of-hospital stroke patients. However, substantial delays in stroke symptom recognition and stroke team activation were observed in patients with a stroke while being hospitalized. Since these delays are likely modifiable, institutions should emphasize targeted interventions to help expedite and expand treatment of in-hospital stroke patients to potentially decrease hospital stays and post-stroke morbidity, such as systematic hospital staff stroke recognition training and dedicated, widely circulated in-hospital acute stroke protocols.

Availability of data and material. Additional data and materials can be made available on reasonable request by a qualified investigator.

Author contributions. PNC: Interpreted clinical data and critically revised the manuscript, with agreement to be accountable for all aspects of the work.

JR: Acquired and interpreted clinical data, with agreement to be accountable for all aspects of the work.

CH: Acquired and interpreted clinical data, with agreement to be accountable for all aspects of the work.

LH: Acquired and interpreted clinical data and drafted the initial manuscript, with agreement to be accountable for all aspects of the work.

GJ: Conceived the manuscript, analyzed the data and critically reviewed the final manuscript.

AYP: Conceived the manuscript, analyzed the data and critically reviewed the final manuscript.

YD: Conceived the manuscript, analyzed the data and drafted the initial manuscript, with agreement to be accountable for all aspects of the work.

AVC: Conceived the manuscript, analyzed the data and drafted the initial manuscript, with agreement to be accountable for all aspects of the work.

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Competing interests. None of the authors report any competing interests.

Ethics approval and consent to participate. This study was conducted after appropriate prior ethical approval from the Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM). No experiments were performed on human participants.

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