Full Title: Differences in and determinants of pre-hospital delay times among stroke patients - 1994 versus 2012

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Short title: Changes in pre-hospital delay among stroke patients

ABSTRACT

Objectives: Pre-hospital delay is a challenge for stroke treatment and the delivery of time-critical treatments. Few studies have examined secular trends in pre-hospital delay, and results vary. This study investigates how pre-hospital delay among Norwegian stroke patients has changed over the last two decades.

Materials & methods: We compared time from symptom onset to admission in two cohorts of stroke patients admitted to Akershus University Hospital, Norway, in 1994 ($n = 550$) and 2012 ($n = 522$), and constructed predictive models for arrival within three hours for each cohort.

Results: More patients arrived within three hours of symptom onset in 2012 compared to 1994 (proportion 47.1% vs 19.3%, $P < .001$), also after adjusting for age, sex and baseline differences; odds ratio 5.14 (95% CI: 3.69 – 7.15). Stroke severity was the only predictor examined that was independently associated with early arrival during both periods. For patients with moderate strokes the overall odds ratio was 2.06 (95% CI: 1.41 – 3.00) and for severe strokes 4.52 (95% CI: 2.97 – 6.87), compared to those with mild strokes. In the 1994-cohort additional predictors of early arrival were living with others, and, not being admitted from nursing home.

Conclusions: Pre-hospital delay in Norway has decreased considerably over the last two decades, and since the availability of time-critical treatments. However, there is still an urgent need to reduce the number of delayed admissions as a large proportion of patients continue to arrive too late to benefit from these treatments. More severe strokes predict earlier arrival.

INTRODUCTION

Stroke is a leading cause of death and disability worldwide.¹ The disease is considered a medical emergency with increasing brain tissue loss the longer the delay to treatment. In addition to organized stroke units (SUs), which are well-established in reducing mortality and dependency,² time-critical treatments exist that reinforce the importance of early hospital admission.

Recombinant tissue plasminogen activator (rt-PA) was first approved for use in stroke in the United States in 1996 following the positive results from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study.³ In Norway, treatment within three hours of ischemic stroke was approved in 2003, and the therapeutic window officially extended to 4.5 hours in 2013, although changes in practice began as early as 2010 after the publication of new evidence-based national treatment guidelines.⁴ Endovascular thrombectomy, a more recent therapeutic advance, has a slightly wider therapeutic window; however, as with thrombolysis, its efficacy diminishes the longer the delay.⁵

Pre-hospital delay, the time interval from symptom onset to presentation to hospital, is an important factor for good outcome among stroke patients due to the highly time-dependent nature of reperfusion therapy. Stroke conveys an added challenge because its symptoms can cause considerable impairment resulting in difficulty seeking help. Symptoms may also be varied or diffuse, and therefore challenging to recognize as stroke. Recent studies⁶⁻⁸ have found that 25–64% of patients arrive to hospital within three hours of symptom onset. A meta-analysis⁹ estimated an annual decrease in pre-hospital delay of 6% between 1981–2007, however a large US study⁶ did not find any time trends between 2003–2009. The temporal trends for pre-hospital delay in Norway are so far not known.

This study investigates how pre-hospital delay times have changed over the last two decades by comparing time from symptom onset to admission in two prospective cohorts of stroke patients admitted to Akershus University Hospital in 1994–95 and 2012–13. A secondary objective was to identify factors related to early arrival during the two time periods.

METHODS

Setting and participants

Akershus University Hospital is situated in the Oslo greater metropolitan area and serves approximately 10% of Norway's population. It is the only hospital admitting patients with suspected stroke in the geographically defined catchment area. National guidelines^{4,10} recommend admitting all patients with symptoms of acute stroke as early as possible, and encourage direct admission without prior examination by a medical doctor. Data on consecutive admissions with stroke meeting the inclusion criteria were prospectively collected between March 1, 1994 – December 31, 1995 (the 1994-cohort), and between February 15, 2012 – March 15, 2013 (the 2012-cohort). Data on the 1994-cohort were originally collected to investigate the effect of SU versus general medical ward care, and have been previously described.¹¹ The 2012-cohort is a subset of the Norwegian Stroke – Paths of Treatment (NOR-SPOT) cohort,¹² collected to investigate delivery of health services to Norwegian stroke patients, and the present study forms part of that project. The same inclusion criteria from 1994 were applied to the 2012-cohort for comparability.

Patients were included if they were aged ≥ 60 years, discharged with a diagnosis of stroke, experienced symptom onset outside of hospital, and were admitted within 24 hours (one calendar day in 2012). The World Health Organization definition of stroke¹³ was used; however patients presenting with symptoms consistent with stroke and treated with

reperfusion therapy resulting in resolution of symptoms before 24 hours were classified as having stroke. Both first-ever and recurrent strokes were included, but only the first admission during the study period.

Outcomes and measures

The primary outcome was *pre-hospital delay*; the time interval from symptom onset to presentation to the hospital. Pre-hospital delay times from the 1994-cohort were available as pre-specified intervals of ≤ 3 hours, 3–6 hours, 6–12 hours, and > 12 hours (but within 24 hours). These same intervals were therefore also calculated for the 2012-cohort (with a maximum of one calendar day for the last time-interval). If the exact time of onset was unknown but an approximate time interval was, the mid-point was used.

Stroke severity on admission was scored prospectively by the neurologist on duty. In the 1994-cohort the Scandinavian Stroke Scale¹⁴ (SSS) was used, and in 2012 the National Institutes of Health Stroke Scale¹⁵ (NIHSS). Both the SSS and NIHSS are reliable and valid measures.^{16–18} Where a prospective NIHSS score was unavailable, the first author (A.S.L.) scored patients retrospectively using admission records and a validated algorithm.¹⁹ For between-cohort comparability, scores were trichotomized using previously published cut-offs^{20,21} into mild (NIHSS 0–7; SSS 43–58), moderate (NIHSS 8–16; SSS 26–42) and severe (NIHSS 17–42; SSS 0–25). Primary stroke type was determined via imaging (ischemic versus hemorrhagic). Reduced consciousness at admission was defined by a score of ≤ 2 on item 1 of the SSS in 1994 and by a Glasgow Coma Scale score of ≤ 10 in 2012, as these were deemed equivalent. A past history of cerebrovascular disease (transient ischemic attack or stroke) and current smoking status was recorded based on self-report and medical records, as was basic demographic information.

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD), and categorical variables as frequency and percentage. Independent samples t-tests were used to test differences between continuous outcomes, and Chi-squared for categorical outcomes. Pre-hospital delay was dichotomized as ≤ 3 hours versus > 3 hours for logistic regression analyses. Adjusted odds ratios (ORs) for between-cohort differences were estimated using binomial logistic regression and the enter method. Patients with unknown symptom onset time were excluded from tests of between-cohort differences in pre-hospital delay. *Post hoc* sensitivity analyses were performed to check the robustness of the results. Predictive models for pre-hospital delay ≤ 3 hours were estimated separately for 1994 and 2012 using logistic regression and Akaike inclusion criteria for model selection. Collinearity was assessed for the predictive multivariable models. Statistical analyses were performed on SPSS version 23.

Ethical considerations

Collection of the 1994-cohort data was approved by the Regional Ethics Committee (REC) (approval number S-93231), and consent obtained prior to recruitment. The NOR-SPOT project was classified as a quality assurance project by REC and therefore, and in accordance with REC's recommendation, ethical approval was granted by the Data Protection Officer at Akershus University Hospital (approval number 11-076). Permission for the use of data from the 1994-cohort for the current study was deemed by REC to fall outside of its mandate since the data was anonymized. Consequently, approval for its use in the current study was granted by the hospital's Data Protection Officer under NOR-SPOT's existing approval number.

RESULTS

A total of 1072 patients were included in this study; 550 patients in the 1994-cohort and 522 in the 2012-cohort. Twenty of the 570 patients originally included in 1994 were subsequently

excluded due to a non-stroke final diagnosis. Of the 724 patients aged ≥ 60 years admitted with stroke in the 2012-cohort, 202 patients were excluded: 3 patients did not wish to participate, 162 were admitted more than one calendar day after symptom onset, 13 were previously included, and 24 experienced symptom onset in hospital or were admitted elsewhere first.

Patients admitted in 2012 were on average 2.4 years older than in 1994 (mean age 78.8 years vs 76.4 years, $P<.001$), Table 1. Similar proportions were female, married, and living alone, however, more patients were admitted from nursing homes in 2012 (10.0% vs 3.5%, $P<.001$). Smoking rates and previous history of cerebrovascular disease remained unchanged. Similar proportions presented with intracerebral hemorrhage and reduced consciousness, however stroke severity was significantly milder in 2012 ($P<.001$).

Patients arrived earlier in 2012 compared to 1994, with 47.1% arriving within 3 hours, compared to 19.3% in 1994 ($P<.001$), Table 2. When patients with unknown symptom onset times were excluded (Figure 1), these proportions increased to 53.1% and 24.2% respectively. Adjusting for confounders (age, sex, stroke severity, and admission from nursing home) showed patients in 2012 still more likely to arrive within 3 hours: odds ratio (OR) 5.14 (95% CI: 3.69 – 7.15). Stroke severity was overall independently associated with pre-hospital delay with severer strokes more likely to present earlier: moderate OR 2.06 (1.41 – 3.00); and severe OR 4.52 (2.97 – 6.87), compared to mild stroke.

Pre-hospital delay was skewed towards earlier arrival within every category of stroke severity in 2012 compared to 1994 (Figure 2). This was most distinct for patients with severe strokes where 83.3% of patients in 2012 arrived within 3 hours, and none arrived after 12 hours. Pre-hospital delay times were significantly different between the cohorts for every stroke severity category ($P<.001$).

Predictive models for arrival within three hours (Table 3) showed that increasing stroke severity was the strongest predictor in both cohorts, and was the only independent predictor in the 2012-cohort. Additional predictors in 1994 were living with others, and not being admitted from nursing home. Pre-hospital delay was also dichotomized according to the maximum recommended times in the respective guidelines^{4,10} (12 hours in 1994, and 6 hours in 2012), resulting in 76.9% in 1994, and 68.3% in 2012 satisfying recommendations ($P=.004$).

More patients in the 1994-cohort had unknown symptom onset times compared to 2012 (20.4% vs 11.3%, $P<.001$). An analysis of patients with known symptom onset times ($n = 901$) versus those without ($n = 171$) showed that the patients with unknown times were less likely to be married (42.7% vs 57.2%, $P<.001$), and more likely to be living alone (45.0% vs 32.0%, $P=.001$), Table 4. *Post hoc* sensitivity analyses were performed to evaluate the effect of different cut-off points than ≤ 3 hours when testing for between-cohort differences, and also to adjust for all remaining baseline patient and clinical characteristics in case of missed confounding effects. Neither of these analyses were significant (results not shown).

DISCUSSION

Pre-hospital delay times have improved considerably between 1994 and 2012 among Norwegian stroke patients aged 60 years and over, with 47.1% arriving within three hours in 2012, compared to 19.3% in 1994. There was a general shift towards earlier admission in 2012, and increasing stroke severity was an independent predictor of early admission in both cohorts.

Our findings in the 2012-cohort reflect recent studies⁶⁻⁸ of pre-hospital delay times in patients with stroke or stroke-like symptoms, which report 25–64% arriving within three hours of

symptom onset. Only 19.3% of patients in 1994 arrived within three hours, which likely reflects the evidence-based knowledge at the time. Treatment with thrombolysis was then, in Norway, limited to clinical trials, and the clinical guidelines¹⁰ recommended hospital admission within 12 hours at the latest; which 76.9% of patients accomplished. Nonetheless, the proportion of patients arriving early in the 1994 cohort is relatively low compared to other studies²²⁻²⁴ conducted during the same time period which report 24–60% arriving within three hours.

There is a paucity of existing studies examining temporal trends in pre-hospital delay times. A study⁶ using data from the Get With the Guidelines-Stroke program did not find any significant trends over time (2003–2009). However, a systematic review⁹ of papers published between 1981–2007 found that pre-hospital delay has decreased over time. The authors estimated an annual decline in median pre-hospital delay of 6.0%; however, this had slowed in the more recent years. Studies published after 2000 reported median delay times of between three and four hours. Although pre-hospital delay times have improved, the narrow therapeutic window for reperfusion therapy means that a large proportion of patients are still unable to be considered for these interventions.

Multivariable analysis showed that more severe strokes were independently associated with early arrival, as numerous studies have also shown.^{7,24-27} Ambulance transport to hospital is another factor strongly related to reduced pre-hospital delay,^{22,23,26,27} however was unfortunately unavailable for our analysis. Other factors previously shown to be associated include living with others,²⁴ carotid territory stroke,²⁶ and self-referral²⁵ (compared to nursing home or general practitioner referral), although results do vary. Living with others, and admission from home (versus nursing home), were related to early arrival in 1994 only, but neither the presence of stroke risk factors, or previous cerebrovascular disease were

significant in either cohort. A scientific statement on pre-hospital delay in ischemic stroke by the American Heart Association²⁸ supports these findings, as do several other studies.^{22,24,26,27}

Various media campaigns, such as the Face-Arm-Speech-Time (FAST)²⁵ campaign, have tried to increase stroke awareness by highlighting common symptoms and the time-critical nature of the disease. Unfortunately, these campaigns have generally not been shown to increase early arrival, although they may be effective in improving knowledge of stroke symptoms.^{7,25} This is in keeping with findings that previous knowledge of stroke does not necessarily imply earlier arrival,^{22,29} possibly due to patients' failure to recognize their symptoms as stroke, or hesitation in seeking medical assistance.²² Interestingly, stroke severity was significantly milder in 2012 compared to 1994. Better primary and secondary prevention could have resulted in a shift in incidence from severe to mild strokes. It is also possible that fewer patients with very mild strokes were admitted to hospital in 1994.

Strengths of this study include that the patients were prospectively recruited, and were all admitted to the same hospital which has a large and diverse catchment area. During both periods national policy has been to admit patients as early as possible and directly without prior medical examination. The hospital is the only in the region admitting stroke patients, resulting in an unselected source population. Recruitment was virtually complete; all patients approached in 1994 consented to inclusion, and data collection in 2012 was considered quality assurance and therefore did not formally require consent. The long interval between the cohorts (18 years) allows for an interesting comparison of the pre- and post-thrombolysis eras, and is the longest interval for this type of study as far as we know.

Generalizability is limited by the inclusion criteria from 1994 of patients aged 60 years and over. The majority of stroke patients are, however, within this age group. There are other limitations to this study; pre-hospital delay was only able to be examined categorically, and

limited to admissions within 24 hours; however this would not alter the study's conclusion. A restricted number of explanatory variables were available for the analysis of factors related to delay, and only two time periods could be compared. Several patients had unknown symptom onset times, the majority in the 1994-cohort. A sensitivity analysis showed that these patients were less likely to be married, and more likely to be living alone. It is possible that the non-symmetrical distribution of these patients between the cohorts biased the results; however, any bias would be expected to strengthen the conclusion, as these highly correlated factors were associated with later arrival in the 1994-cohort. These challenges are not unique, and previous studies on pre-hospital delay have also had to exclude patients with unknown symptom onset, or truncate inclusion times.^{6-8,24}

It is positive that pre-hospital delay in stroke has decreased over time in Norway, and since the introduction of time-critical and effective interventions; however a substantial proportion of patients still arrive too late to benefit. Media campaigns have generally not been shown to be effective in decreasing pre-hospital delay times, and there remains a critical need to identify and implement measures to reduce the number of delayed admissions.

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CONFLICTS-OF-INTEREST: None.

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FIGURE LEGENDS

Figure 1. Proportion of patients arriving within different time intervals in 1994 versus 2012

Patients with unknown symptom onset times excluded. Overall $P < .001$.

Figure 2. Distribution of pre-hospital delay times within categories of stroke severity in 1994 and 2012

Between-cohort difference for delay times is $P < .001$ for every stroke severity category, when each category analyzed separately. Patients with unknown symptom onset times excluded.

TABLES

Table 1. Patient characteristics at admission

Characteristic	1994-cohort (<i>n</i> =550)		2012-cohort (<i>n</i> =522)		<i>P</i>
Mean age, years	76.4	(7.2)	78.8	(9.3)	<.001
Female sex	258	(46.9)	256	(49.0)	.49
Married or partner	305	(55.5)	283	(54.2)	.68
Living alone	184	(33.5)	181	(34.7)	.67
Admitted from nursing home	19	(3.5)	52	(10.0)	<.001
History of cerebrovascular disease	208	(37.8)	189	(36.2)	.59
Current smoker	120	(21.8)	103	(19.7)	.40
Hemorrhage on CT	66	(12.0)	74	(14.2)	.29
Reduced consciousness	51	(9.3)	52	(10.0)	.70
Stroke severity					
Mild	269	(48.9)	347	(66.5)	<.001
Moderate	142	(25.8)	95	(18.2)	
Severe	139	(25.3)	80	(15.3)	

Values expressed as mean (SD), *n* (%).

Table 2. Pre-hospital delay times in 1994 and 2012

	1994-cohort (<i>n</i>=550)	2012-cohort (<i>n</i>=522)	<i>P</i>
≤ 3 hours	106 (19.3)	246 (47.1)	<.001
3 – 6 hours	145 (26.4)	70 (13.4)	<.001
6 – 12 hours	86 (15.6)	66 (12.6)	.03
> 12 hours	101 (18.4)	81 (15.5)	.04
Unknown	112 (20.4)	59 (11.3)	<.001

Values expressed as *n* (%). Patients with unknown delay times excluded from significance tests for between-cohort differences (except category “unknown”).

Table 3. Final models of factors related to hospital admission ≤ 3 hours in 1994 and 2012

Factor	1994-cohort (n=438)	2012-cohort (n=463)
Living alone	0.32 (0.18 – 0.56)	-
Admitted from nursing home	0.20 (0.04 – 0.93)	-
Stroke severity		
Mild	Reference	Reference
Moderate	1.87 (1.05 – 3.33)	2.25 (1.37 – 3.72)
Severe	3.77 (2.17 – 6.53)	6.38 (3.22 – 12.65)

Values expressed as odds ratios (95% CI), adjusted for factors included in the final models.

Models estimated separately for each cohort using multivariable logistic regression and Akaike information criteria for model selection. Variables shown in Table 1 entered into initial models except “Married or partner” which was excluded due to collinearity with “Living alone”. Patients with unknown symptom onset times excluded.

Table 4. Characteristics of patients with known versus unknown symptom onset times

Characteristic	Known symptom onset (<i>n</i>=901)		Unknown symptom onset (<i>n</i>=171)		<i>P</i>
Mean age, years	77.5	(8.3)	78.1	(8.6)	.33
Female sex	423	(46.9)	91	(53.2)	.13
Married or partner	515	(57.2)	73	(42.7)	<.001
Living alone	288	(32.0)	77	(45.0)	.001
Admitted from nursing home	62	(6.9)	9	(5.3)	.44
History of cerebrovascular disease	340	(37.7)	57	(33.3)	.27
Current smoker	187	(20.8)	36	(21.1)	.93
Hemorrhage on CT	122	(13.5)	18	(10.5)	.28
Reduced consciousness	84	(9.3)	19	(11.1)	.47
Stroke severity					
Mild (reference)	523	(58.0)	93	(54.4)	.45
Moderate	200	(22.2)	37	(21.6)	
Severe	178	(19.8)	41	(24.0)	

Values expressed as mean (SD), *n* (%).

FIGURES

Figure 1. Proportion of patients arriving within different time intervals in 1994 versus 2012

Patients with unknown symptom onset times excluded. Overall $P < .001$.

Figure 2. Distribution of pre-hospital delay times within categories of stroke severity in 1994 and 2012

Between-cohort difference for delay times is $P < .001$ for every stroke severity category, when each category analyzed separately. Patients with unknown symptom onset times excluded.