PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Hospital-based cohort study to determine the association between home-time and disability after stroke by age, sex, stroke type, and study year in Canada
AUTHORS	Yu, Amy Ying Xin; Fang, Jiming; Porter, Joan; Austin, Peter; Smith, Eric E.; Kapral, MK

VERSION 1 – REVIEW

REVIEWER	Martin N. Stienen Stanford University Hospital and Clinics, Stanford CA (USA)
REVIEW RETURNED	14-May-2019

GENERAL COMMENTS	The authors determined the association between 90-day post-stroke home-time and the mRS disability outcome at hospital discharge in a large, population-based setting in Canada. They included different types of ischemic and hemorrhagic stroke. They hypothesized that home-time would be strongly associated with the mRS score and that this association would not be significantly modified by stroke type, temporal trends, or patient demographics. Using the Ontario Stroke Registry they were able to identify 39417 stroke patients out of a 13 million population between April 1st 2002 and March 31st 2013. 84% had ischemic stroke, median age was 74 years and the male:female ratio was about 1:1. Median 90-day home-time was 55 days, and more home-time was associated with lower mRS at discharge. Results were consistent for both ischemic and hemorrhagic stroke types. Besides mRS, comorbidity, stroke severity (NIHSS) and baseline functional status were associated with home-time. Furthermore, for almost all levels of the mRS (except those with the most severe disability), older patients experienced less home-time compared to younger patients. As the authors correctly point out, home time is dependent on the structures of the health care system, and as such further data is needed. Strengths and weaknesses of their article are correctly pointed out and discussed adequately. I would like to congratulate the authors to their important and well-written article. Please find below some comments that they might find valuable to consider. Comments: - The authors write that home-time was correlated to mRS for ischemic stroke. Besides ischemic stroke types, home-time was recently validated for SAH as hemorrhagic stroke type in a Swiss nationwide sample. It was even shown to correlate with 1-year mRS outcome, illustrating that it can even be used to extrapolate

longer-term disability (compare Stroke. 2018 Dec; 49(12):3081-3084. doi: 10.1161/STROKEAHA.118.022808) As home-time was shown to correlate with mRS outcome in the setting of SAH, it has been included as one of the recommended outcome measures for SAH by the NIH/NINDS common data elements group. I understand that research about this outcome measure is ongoing and the authors might not have been aware of this when composing their work, but I would be interested to understand why they chose to exclude SAH patients for this analysis. I acknowledge that outcome after SAH is different than outcome after other stroke types, owing to the younger patient population with both focal and disseminated injury of the brain, but including SAH in this study would represent a strength in my opinion.
- Ontario public home care services were registered in order to obtain information on patients who live home, but require considerable assistance. How was this dealt with for analysis purpose? The mRS of patients discharged home early but with considerable home support might be higher than the mRS of patients with longer hospitalization and independent functional status at discharge.
- Who did the mRS grading? Residents? Attendings? APPs or nursing staff? The mRS is known to have inter-rater reliability issues, which can improve after training and certification. It would be important to understand who made the mRS grading.

REVIEWER	Martin Dennis University of Edinburgh, UK
REVIEW RETURNED	20-May-2019

GENERAL COMMENTS	I think this paper adds usefully to the growing literature on the use of hometime as a measure of stroke outcome. The authors refer to population based cohort, but I am unclear what they mean by this. They have only included hospital admitted patients, so exclude all patients who were not admitted after their stroke. I am therefore unclear what population they are referring to? I would have simply referred to a hospital admission cohort? In abstract it would be helpful to know what measure of disability was used, and at what time point. So mention modified Rankin scale at discharge from acute care facility Need to spell out Institute for Clinical Evaluative Sciences (ICES), when first used In clinical trials which collect outcome data at a defined interval after stroke or admission or randomisation then a direct comparison between 90 day hometime is easily interpreted. As the authors acknowledge in this study they only had the mRS measured at the time of discharge from the acute care facility. This is sub optimal, but in interpreting this it would be useful to know what the distribution of intervals from admission to hospital with stroke to the discharge mRS was. This is available in table 1 (median 9 days) but might be usefully highlighted in the text.

REVIEWER	Peter Langhorne University of Glasgow
REVIEW RETURNED	29-May-2019

GENERAL COMMENTS	I read this article with interest as it addresses the important topic of measuring disability in routine datasets. Overall, I think the study has been carried out to a high standard but I have a few questions and comments.

	1 Materials and methods (page 6) – what does the term ICES mean?
	2 Materials and methods (page 6) – why was severity dichotomised and not used as a continuous variable? This is an unusual way to handle such a variable.
	3 Materials and methods – were TIAs included in the register?
	4 Results (page 10) – how can you explain an interaction with the year of study (please see discussion).
	5 Discussion (page 10) – in the discussion you report that this is the first study to include intracerebral haemorrhage. However, ICH was included in a recent paper by Quinn et al in Stroke.
	6 Discussion (page 11) – what are your explanations for the differences between men and women and older and younger patients. Does this reflect severity of disability or alternative support available?
	7 Discussion – it would be useful to have some brief explanation of what you believe that home-time measures. Is it a proxy for disability, home support, or stroke service quality?
	I hope these comments are useful.

REVIEWER	silvio tafuri
	Department of Biomedical Science and Human Oncology, Aldo Moro University of Bari
REVIEW RETURNED	20-Sep-2019

GENERAL COMMENTS	Dear Editor, with the regards of statistical methods used in the manuscript, I have not important concerns.
	In the abstract, the use of aRR could be hard to understand, because it was not explained.
	In the methods, please clarify that quantitative data were also reported as Mean(SD) (see table 2).
	Please, state the p value considered as significant.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Martin N. Stienen
Institution and Country: Stanford University Hospital and Clinics, Stanford CA (USA)
Please state any competing interests or state 'None declared': None declared.

Comment 1: The authors determined the association between 90-day post-stroke home-time and the mRS disability outcome at hospital discharge in a large, population-based setting in Canada. They included different types of ischemic and hemorrhagic stroke. They hypothesized that home-time would be strongly associated with the mRS score and that this association would not be significantly modified by stroke type, temporal trends, or patient demographics. Using the Ontario Stroke Registry they were able to identify 39417 stroke patients out of a 13 million population between April 1st 2002

and March 31st 2013. 84% had ischemic stroke, median age was 74 years and the male:female ratio was about 1:1. Median 90-day home-time was 55 days, and more home-time was associated with lower mRS at discharge. Results were consistent for both ischemic and hemorrhagic stroke types. Besides mRS, comorbidity, stroke severity (NIHSS) and baseline functional status were associated with home-time. Furthermore, for almost all levels of the mRS (except those with the most severe disability), older patients experienced less home-time compared to younger patients. As the authors correctly point out, home time is dependent on the structures of the health care system, and as such further data is needed. Strengths and weaknesses of their article are correctly pointed out and discussed adequately. I would like to congratulate the authors to their important and well-written article. Please find below some comments that they might find valuable to consider.

Authors' response: Thank you for reviewing our work and for providing constructive comments.

Comment 2: The authors write that home-time was correlated to mRS for ischemic stroke. Besides ischemic stroke types, home-time was recently validated for SAH as hemorrhagic stroke type in a Swiss nationwide sample. It was even shown to correlate with 1-year mRS outcome, illustrating that it can even be used to extrapolate longer-term disability (compare Stroke. 2018 Dec; 49(12):3081-3084. doi: 10.1161/STROKEAHA.118.022808) As home-time was shown to correlate with mRS outcome in the setting of SAH, it has been included as one of the recommended outcome measures for SAH by the NIH/NINDS common data elements group. I understand that research about this outcome measure is ongoing and the authors might not have been aware of this when composing their work, but I would be interested to understand why they chose to exclude SAH patients for this analysis. I acknowledge that outcome after SAH is different than outcome after other stroke types, owing to the younger patient population with both focal and disseminated injury of the brain, but including SAH in this study would represent a strength in my opinion.

Authors' response: We agree with the reviewer that subarachnoid hemorrhage is an important stroke subtype. In addition to what the reviewer already mentioned in terms of differences from other stroke types in patient demographics and mechanism of brain injury, patients with subarachnoid hemorrhage also have different etiologies (aneurysmal, traumatic, other), severity scores (Hunt and Hess scale), management (surgical vs medical), and complications (hydrocephalus, vasospasm) that deserves dedicated analyses and discussion. Instead, we have now added the Stienen et al. paper as a new reference (#25) in the discussion (page 11, paragraph 1): "A recent study reported that discharge mRS is associated with 90-day home-time after admission for aneurysmal subarachnoid hemorrhage."

Comment 3: Ontario public home care services were registered in order to obtain information on patients who live home, but require considerable assistance. How was this dealt with for analysis purpose? The mRS of patients discharged home early but with considerable home support might be higher than the mRS of patients with longer hospitalization and independent functional status at discharge.

Authors' response: We described in Table 1 that 5% of the patients in the cohort were home with home care and 58% were home without home care at 90 days. In the analysis of home-time, patients were considered at home when they were not in any health care institution, regardless of use of home care because the Ontario public home care services are universally available. Thus, we do not expect a patient with high mRS to be discharged home early with home care services compared to another patient with relatively lower mRS to be discharged home later without home care services. As we described in the discussion (page 13, paragraph 1), home care services "may range from a few hours a week to a few hours a day for assistance with activities of daily living or instrumental activities of daily living, but these do not include around the clock support." Further, we acknowledged that

returning home may be contingent on social support or private funds, which are not captured in the administrative data (page 12, paragraph 2).

Comment 4: Who did the mRS grading? Residents? Attendings? APPs or nursing staff? The mRS is known to have inter-rater reliability issues, which can improve after training and certification. It would be important to understand who made the mRS grading.

Authors' response: We agree this should be clearly described and have now added in the methods (page 6, paragraph 2): "Data on discharge mRS were collected in the registry through retrospective chart abstraction by trained abstractors, mainly nurses, with stroke expertise (<1% missing data)."

Reviewer: 2
Reviewer Name: Martin Dennis
Institution and Country: University of Edinburgh, UK
Please state any competing interests or state 'None declared': None declared

Comment 1: I think this paper adds usefully to the growing literature on the use of hometime as a measure of stroke outcome. The authors refer to population-based cohort, but I am unclear what they mean by this. They have only included hospital admitted patients, so exclude all patients who were not admitted after their stroke. I am therefore unclear what population they are referring to? I would have simply referred to a hospital admission cohort?

Authors' response: We agree with the reviewer and have changed the term "population-based cohort" to "hospital-based cohort" in the abstract and manuscript text. We initially described our sample as a population-based cohort because we included all patients admitted to regional stroke centres and a simple random sample of patients from all other hospitals across the province of Ontario. This sampling strategy reduces selection bias compared to using a convenience sample of patients or facilities or performing secondary analyses in patients enrolled in clinical trials.

Comment 2: In abstract it would be helpful to know what measure of disability was used, and at what time point. So mention modified Rankin scale at discharge from acute care facility

Authors' response: We have now added this information in the abstract (page 2): "Association between 90-day home-time, defined as the number of days spent at home in the first 90 days after stroke, obtained using linked administrative data, and modified Rankin Scale score at discharge."

Comment 3: Need to spell out Institute for Clinical Evaluative Sciences (ICES), when first used.

Authors' response: Thank you for this comment. The acronym used to stand for "Institute for Clinical Evaluative Sciences", but the organization formally re-branded to the initialism ICES in 2018 and therefore is no longer spelled out. We added a new reference (#13) that includes a link to the ICES website for clarity: https://www.ices.on.ca/.

Comment 4: In clinical trials which collect outcome data at a defined interval after stroke or admission or randomisation then a direct comparison between 90 day home-time is easily interpreted. As the authors acknowledge in this study they only had the mRS measured at the time of discharge from the acute care facility. This is sub optimal, but in interpreting this it would be useful to know what the distribution of intervals from admission to hospital with stroke to the discharge mRS was. This is available in table 1 (median 9 days) but might be usefully highlighted in the text.

Authors' response: We agree with the reviewer and have now highlighted this information in the first paragraph of the results section (page 8, paragraph 3): "The median in-hospital length of stay was 9 days (5,18)."

Reviewer: 3
Reviewer Name: Peter Langhorne
Institution and Country: University of Glasgow
Please state any competing interests or state 'None declared': None declared

Comment 1: I read this article with interest as it addresses the important topic of measuring disability in routine datasets. Overall, I think the study has been carried out to a high standard, but I have a few questions and comments.

Authors' response: Thank you.

Comment 2: Materials and methods (page 6) – what does the term ICES mean?

Authors' response: The acronym used to stand for "Institute for Clinical Evaluative Sciences", but the organization formally re-branded to the initialism ICES in 2018 and therefore is no longer spelled out. We added a new reference (#13) that includes a link to the ICES website for clarity: https://www.ices.on.ca/.

Comment 3: Materials and methods (page 6) – why was severity dichotomised and not used as a continuous variable? This is an unusual way to handle such a variable.

Authors' response: We agree with the reviewer that handling stroke severity as a continuous variable is usually preferred. However, we were also interested in looking at whether home-time was responsive to covariates known to be associated with stroke outcomes, such as age, premorbid dependence, baseline stroke severity among other variables. We presented the adjusted summary rate ratio of home-time stratified by these clinically relevant predictor variables using ZINB models in Table 2. We acknowledge that stroke severity could be categorized in various ways (binary, terciles, quintiles, etc...). We dichotomised this variable into mild versus severe because these are common categories in clinical practice and the median NIHSS score in our cohort was 5. Splitting into smaller categories may lead to difficulties in interpretation. For example, a NIHSS=12 could be used to describe different clinical deficits, but it is generally accepted that NIHSS < 5 represents a milder stroke compared NIHSS of 5 or more.

Comment 4: Materials and methods – were TIAs included in the register?

Authors' response: Patients with transient ischemic attacks were included in the Ontario Stroke Registry, but in the current study, we only included patients with ischemic stroke or intracerebral hemorrhage (methods, page 5, paragraph 2).

Comment 5: Results (page 10) – how can you explain an interaction with the year of study (please see discussion).

Authors' response: We agree that the test for interaction by study year was statistically significant (p<0.05). However, on page 11, paragraph 1, we explained that "despite a statistically significant p-value for interaction, we did not observe any consistent or clinically meaningful trends in effect modification" by study years. We also referred to the Supplemental Figure 1 showing a forest plot with

the adjusted summary rate ratio for 90-day home-time by mRS by study year with year 2007 as the reference group to support our explanation.

Comment 6: Discussion (page 10) – in the discussion you report that this is the first study to include intracerebral haemorrhage. However, ICH was included in a recent paper by Quinn et al in Stroke.

Authors' response: We have referenced the paper by McDermid, Barber… and Quinn, Stroke 2019 that the reviewer mention in our manuscript (#27). In the discussion, we edited our sentence (page 11, paragraph 1) to clarify that it is the association between home-time and mRS that has not been previously reported in this population: "the association between home-time and mRS has not yet been reported in patients with intracerebral hemorrhage."

Comment 7: Discussion (page 11) – what are your explanations for the differences between men and women and older and younger patients. Does this reflect severity of disability or alternative support available?

Authors' response: The reviewer is correct that the association between discharge mRS and 90-day home-time was modified by sex and age. We discussed that the magnitude of the effect modification by sex is small and unlikely to be clinically significant (page 11, paragraph 1). We also discussed that the interaction by age is likely influenced by comorbid medical illnesses, post-stroke complications, and higher pre-stroke dependence (page 11, paragraph 2). We acknowledged that the availability of alternative support may influence home-time, but we do not have access to these data in the current study (page 12, paragraph 2).

Comment 8: Discussion – it would be useful to have some brief explanation of what you believe that home-time measures. Is it a proxy for disability, home support, or stroke service quality?

Authors' response: We agree with the reviewer that home-time can be used as a proxy for disability. In the concluding paragraph (page 13, paragraph 2), we wrote: "Home-time is associated with global disability after ischemic stroke and intracerebral hemorrhage. Its key advantage is that it can be calculated using routinely collected administrative data, allowing for the measurement of stroke outcomes for large populations."

Reviewer: 4
Reviewer Name: Silvio Tafuri
Institution and Country: Department of Biomedical Science and Human Oncology, Aldo Moro University of Bari
Please state any competing interests or state 'None declared': None declared

Comment 1: Dear Editor, with the regards of statistical methods used in the manuscript, I have not important concerns. In the abstract, the use of aRR could be hard to understand, because it was not explained.

Authors' response: We agree that the adjusted rate ratio may be difficult to understand. Due to limitations in the abstract word count, we felt the best place to describe the interpretation of the adjusted rate ratio was in the methods: "… adjusted rate ratio is interpreted as the ratio of the mean number of home-time days among those exposed to the covariate of interest to the mean number of home-time days among those who were not."

Comment 2: In the methods, please clarify that quantitative data were also reported as Mean(SD) (see table 2).

Authors' response: We have now included this in the methods (page 7, paragraph 2): "Patient characteristics were described using proportions for categorical variables, mean and standard deviation (SD), and median…"

Comment 3: Please, state the p value considered as significant.

Authors' response: We have now clarified this in the methods (page 8, paragraph 1): "If a statistically significant interaction was present (defined as $p<0.05$),…"

VERSION 2 – REVIEW

REVIEWER	Martin Stienen Stanford University USA
REVIEW RETURNED	03-Oct-2019

GENERAL COMMENTS	Thanks for the revisions. In my opinion a valuable contribution to the existing literature.