PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Is length of time in a stroke unit associated with better outcomes for patients with stroke in Australia? An observational study
AUTHORS	Busingye, Doreen; Kilkenny, Monique; Purvis, Tara; Kim, Joosup; Middleton, Sandy; Campbell, Bruce; Cadilhac, Dominique

VERSION 1 – REVIEW

REVIEWER	Javier Mar Alto Deba Hospital, Mondragón, Spain
REVIEW RETURNED	18-Mar-2018

| GENERAL COMMENTS | Review BMJ Open
Introduction
The authors fail to explain the rationale of the study. They aimed to investigate outcomes and factors associated with patients with acute stroke spending at least 90% of their admission in a SU, compared to those having less time in the SU. The problem is that pertaining to one of these two groups of patients is related not to the discrete choice of the neurologists but to their evolution. Thus, authors are comparing outcome in two clinically different groups of patients. The lack of addressing this point undermines the validity of the whole study. Length of stay in the stroke unit can be an indicator of good care but it is also an indicator of clinical heterogeneity.
Methods
In an observational study propensity score (PS) could have been used to reduce the bias associated to the lack of randomization. PS could help to balance the base characteristics of both groups to help a better understanding and interpretation of the different outcomes.
Results
It is clear that "Patients who spent at least 90% of their admission in a SU were more likely to be independent on discharge and less likely to have any severe complication or die in the hospital". The problem is to know if those stroke patients who suffer complications spend more time in-hospitalized in a general ward. In that case, an enlarged LES is the consequence of the bad evolution. If "Median LOS for patients who spent at least 90% of their admission in a SU was two days shorter than for those who did not" we can hypothesize that all patients stay a fixed number of days in the SU but those who complicate remain more time in the general ward. The "dose effect between occurrence of any severe complications and percentage of admission spent in a SU" is also explained by the same mechanism.
Discussion
When the authors state that "Spending at least 90% of admission in a SU was associated with fewer severe complications compared to lower proportions of time spent in a SU and these data provide support for the 90% benchmark" they do not discuss at any time the |

	need to define the basal clinical features and the key problem of the causal relationship. A shorter LOS is a consequence of the positive evolution and not its cause. This work should be reoriented taking into account the bidirectional relationship between LES and clinical complications.

REVIEWER	Brian Buck Division of Neurology, University of Alberta, Canada
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	The manuscript is an observational study using cross-sectional data from 2015 Australian audit program. The main goal of the analysis is to compare outcomes and factors associated with stroke patients spending >90% vs <90% of their admission in an organized stroke unit (SU). The main finding is that spending at least 90% of admission in an SU is associated with better patient outcomes. The study is well written and uses a large national dataset with a standardized collection method. Comments: 1) I think there needs to be a brief clarification about how patients typically flow through a hospital in Australia, specifically with respect to total time on a stroke unit. What would typically cause a patient to have a stroke unit admission of between 1-90% vs >90%? For example, is the usual practice that patients with severe stroke with limited rehabilitation potential or requiring palliation more likely to be admitted to a general medicine unit? Do patients get moved off a stroke unit when waiting for long-term care? Is that an alternate explanation for why patients with >90% time on SU have lower rates of discharge to "aged care" (Table 2) Also, does the admission time start once the patient arrives in the ED or on transfer to the stroke or medicine unit? Are patients going to a general medicine unit first then getting a CT scan then going to a stroke unit? Understanding some of the above issues would help with the generalizability of these finding to other healthcare systems. 2) The main limitation when interpreting the patient outcomes between the two groups is that the baseline stroke severity is not measured, and other comorbidities are not the same between the >90% and <90% groups. The final paragraph in the discussion (start 317) does not really discuss prominently the important of stroke severity. In this study, like many administrative datasets, there is no measurement of admission stroke severity between the two groups other than to use indirect measures such as the ability to walk. More specifically, there is no admission NIHSS. This should be discussed as a limitation.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Introduction

The authors fail to explain the rationale of the study. The problem is that pertaining to one of these two groups (spending at least 90% of time in a SU compared to having less time in a SU) of patients is related not to the discrete choice of the neurologists but to their evolution. The lack of addressing this point undermines the validity of the whole study.

Thank you for this suggestion. We have expanded the introduction to further acknowledge additional factors that may influence the time a patient spends in the SU and the rationale for undertaking this study.

"*Various factors can affect the time that patients spend in a SU. These factors include the bed capacity of the SU,[7] bed management decisions,[8, 9] hospital policies, delays in the emergency department,[10] the clinical acuity of the patient whereby intubation or management in intensive care is warranted,[11] or delayed discharges for the next stage of care (e.g. inpatient rehabilitation, or aged care facility). Within Australia and in other counties, it has been recommended that 'spending at least 90% of the hospital admission in a SU' is an important indicator of high quality acute stroke care.[12-14] However, there is limited evidence that the proportion of time spent in the SU is associated with better outcomes in patients with stroke. In an observational study using data from the United Kingdom National Sentinel Audit of Stroke, lower case fatality was associated with spending more than 50% of hospital stay in the SU.[15] Specific evidence is lacking relating to the benefits of spending 90% or more of the admission in a SU. In our study, we aimed to investigate in-hospital patient outcomes, and determine factors associated with patients with acute stroke spending at least 90% of their admission in a SU, compared to those having less time in the SU*" (page 4, last paragraph).

Methods

In an observational study propensity score could have been used to reduce the bias associated to the lack of randomization, balance the base characteristics of both groups and help to better understand and interpret the different outcomes

As suggested, we performed propensity score matching to minimise potential confounding by indication as sensitivity analyses. The following has been added to the methods section (page 8, paragraph 2)

"*Additional sensitivity analyses were undertaken, including:*

> i) *propensity score matching with stratification to minimise potential confounding by indication and compare between similar subgroups of patients (see Supplemental Methods)*"

A sentence regarding the results of the propensity score matching has also been added to the results (page 13, paragraph 1) "*Results from the sensitivity analyses using propensity score matching*

provided evidence of benefit from a greater proportion of time spent in a SU when confounding by indication is controlled (Supplemental Tables C and F). These results are consistent with our findings from the primary analysis" with full methodology and results provided in the Supplemental material.

A sentence has also been added to paragraph 1 of the discussion (page 16) "*Similar results were evident from the primary analyses using the whole sample and propensity score matching, leading to more confidence in the validity of results.*"

Results

It is clear that 'Patients who spend at least 90% of their admission in a SU were more likely to be independent on discharge and less likely to have any severe complications or die in hospital". The problem is to know if those stroke patients who suffer complications spend more time in-hospitalized in a general ward. In that case, the enlarged LOS is the consequence of the bad evolution.

You raise a valid point. In an effort to address whether the length of stay was increased in patients who experienced a severe complication, we have added additional data to Table 2 reporting 'Length of stay (if severe complications) and Length of stay (no severe complication)" and referred to these results (page 13, paragraph 2) "*No difference in median LOS between groups for those patients who experienced a severe complication (Table 2)*"

Discussion

The authors that 'Spending at least 90% of admission in a SU was associated with fewer complications compared to lower proportions of time spent in a SU and these data provide support for the 90% benchmark', but they do not discuss the need to define the basal clinical features and the key problem of the causal relationship. A shorter LOS is a consequence of the positive evolution and not its cause. This work should be reoriented taking into account the bidirectional relationship between LOS and clinical complications.

To avoid ambiguity, we have removed the sentence "*Spending at least 90% of admission in a SU was associated with fewer complications compared to lower proportions of time spent in a SU and these data provide support for the 90% benchmark*" which related to the second sensitivity analyses.

We have added the following to further acknowledge that the study only shows association rather than causality (page 17, paragraph 2) "*We acknowledge that given the study design we cannot make*

inferences about causality. Clinically, a longer LOS may be a consequence of experiencing a severe complication (as by definition may increase time in hospital), a more severe form of stroke, or delays in access to the next stage of care. Although more patients with a severe complication were not treated in a SU, for those who did access SU care, there was no difference in LOS for those who experienced a severe complication based on the proportion of time spent in the SU."

Reviewer 2

I think there needs to be a brief clarification about how patients typically flow through a hospital in Australia, specifically with respect to total time on a stroke unit. What would typically cause a patient to have a stroke unit admission of between 1-90% and >90%. Do patients get moved off a stroke unit when waiting for long-term care?

These are very useful suggestions, thank you. We have added further detail in the introduction to provide readers with additional information relevant to the context of the study and the potential factors that may affect the length of time patients spend in Australian acute stroke units (see comment to Reviewer 1).

A section titled 'Context of acute stroke care' has also been included in the Methods, to outline the flow through Australian hospitals (page 5).

Context of acute stroke care

In Australia, the majority of patients with stroke are managed in public hospitals. It is usual practice that patients with suspected stroke or transient ischaemic attack present to the emergency department of hospitals, and are rapidly assessed, with brain imaging performed as a priority. Generally, all patients should be admitted to an acute SU, or medical ward if the hospital has no available beds in the SU or does not have a SU or neurology ward. If patients require intubation or require higher acuity monitoring and one-to-one nursing care, they may also be managed in an intensive care unit. The median length of stay in the acute setting is 5 days (Q1, 2; Q3, 8),[17] after which, if rehabilitation is required, it is either provided in a separate subacute rehabilitation ward or hospital, or in a community setting.

To address the lower proportion of discharges to aged care facilities, an additional line has been included in the results (page 13, paragraph 1);

"*Patients discharged to aged care were more likely to be transferred from the SU to another ward/unit before being discharged from hospital regardless of how long they spent in the SU (Discharged aged care: 60% were discharged from the SU the same day as from hospital; other destination: 84%).*"

and to the discussion (page 17) "*The reduced likelihood of discharge to residential aged care facility for those spending >90% of time in the SU is potentially resultant from transfers to other wards when waiting for longer-term care.*"

Also does admission time start once the patient arrives in the ED or on transfer to the stroke/medical unit? Are patients going to a general medical unit first then getting a CT scan then going to a stroke unit? Understanding these issues would help with generalizability of these findings to other healthcare systems

To make it clear for the reader, we have added some additional detail about the admission time (page 6, paragraph 2) "*To determine patients who spent at least 90% of their admission in a SU, the SU time was divided by total length of stay (LOS) in the hospital (total LOS; calculated by subtracting date of discharge from hospital or death from date of admission to hospital. This corresponds to the admission to the respective acute care ward, or commencement of an episode of care)…*"

Detail to assist with understanding the context, and therefore generalisability of the findings has been added as outlined in the response above, with an additional line included in the first paragraph of the discussion "*While results are based on stroke care provided in Australian hospitals, these findings are important for promoting and ensuring that patients with stroke spend most of their acute hospital stay in a SU and can be generalised to other countries with similar models of stroke care.*"

The main limitation when interpreting the patient outcomes is that the baseline stroke severity is not measured, specifically there is no NIHSS, and other comorbidities are not the same between the two groups.

Unfortunately, the NIHSS is not collected in the Stroke Audit. However, as a surrogate for stroke severity, we used the four indicators of arm weakness, speech disturbance and inability to walk on admission, and incontinence within 72 hours of onset, which are based on a validated prognostic model (Counsell et al, Predicting outcome after acute and subacute stroke: development and validation of new prognostic models. Stroke. 2002;33(4):1041-7), and have been shown to perform just as well as other recommended models that include age and the National Institutes of Health Stroke Scale (Sim et al. Validation and Recalibration of Two Multivariable Prognostic Models for Survival and Independence in Acute Stroke. PLoS One 2016;11(5):e0153527). These severity indicators were included in all our models, as outlined in the statistical analysis section of the methods (page 8, paragraph 1) "*Other potential confounders including stroke type (ischemic vs intracerebral heamorrhage and unknown) and stroke severity factors such as inability to walk, arm weakness, and*

speech impairment on admission and incontinence within 72 hours, which are based on the Counsell et al validated prognostic model for comparing patient outcomes,[19] were included. This validated model[19] has been compared against a model using age plus scores on the National Institutes of Health Stroke Scale and both prognostic models performed well overall, thus the choice between them should be based on clinical and practical considerations.[20]" as well as the footnotes for Table 2 (page 14) which presents the outcomes for the multivariable modelling.

The final paragraph in the discussion does not discuss the importance of stroke severity and this should be discussed as a limitation

We do agree that there are limitations with the use of cross sectional data, especially in the alibility to draw temporal conclusions and adjust for all potential confounders. This was outlined initially in the Discussion, but has been further been expanded (page 19) "*The comprehensive dataset did allow us to adjust our multivariable models for a number of comorbidities and patient variables, including stroke severity, for which we used a validated prognostic model. However, we acknowledge that the influence of unmeasured confounders such as socioeconomic status, and other comorbidities could*

VERSION 2 – REVIEW

REVIEWER	Javier Mar Hospital Alto Deba, Clinical Management Unit
REVIEW RETURNED	08-Jun-2018

GENERAL COMMENTS	The authors have responded adequately to the comments from the first review.

REVIEWER	Brian H Buck University of Alberta, Canada
REVIEW RETURNED	22-Jun-2018

GENERAL COMMENTS	The authors have done an excellent job addressing the issues identified in my initial review of the manuscript. This revised version of the manuscript is substantially improved.