PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Rural-urban differentials in 30-day and 1-year mortality following first-ever heart failure hospitalisation in Western Australia: A population-based study using data linkage
AUTHORS	Teng, Tiew-Hwa Katherine; Katzenellenbogen, Judith; Hung, Joseph; Knuiman, Matthew; Sanfilippo, Frank; Geelhoed, Elizabeth; Hobbs, Michael; Thompson, Sandra

VERSION 1 - REVIEW

REVIEWER	Warren Laskey MD, MPH University of New Mexico United States of America
REVIEW RETURNED	17-Feb-2014

GENERAL COMMENTS	Although the urban-rural disparity of outcome has been previously described, I wonder whether there is more useful information here. The authors have collapsed 5 distinct geographic regions into 2 (rural, urban) with a resultant loss of variance for the variable "place". Since the 5 regions represent geographic clusters, the data need to be adjusted for the correlation of outcomes within clusters, In other words, perhaps a hierarchical approach is more appropriate here and perhaps the 95% CIs, when appropriately adjusted, might then include 1.0. I am struck by how little the addition of covariates beyond age, sex, period add to the strength of the association. The 95% CIs overlap despite the numerical increase in the point estimates. Did tests for additional information (AIC, BIC, likelihood ratio) substantiate significant differences beyond the first model?

REVIEWER	Jack Tu ICES Sunnybrook Hospital University of Toronto Canada
REVIEW RETURNED	28-Feb-2014

GENERAL COMMENTS	This paper compared the outcomes of heart failure patients hospitalized in Western Australia using a linked adminsitrative data set between those from urban and rural areas. The primary conclusion is that the survival is worse for those who live in rural areas, after adjustment for available confounding variables. The paper is generally clearly written. The major limitation of the paper is that the authors do not appear to have any additional infomration to help explain they the disparities in outcomes exists. 1) The authors used the Charlson index as their measure of

	comorbidity severity. There are more sophisticated administrative models avaialble for assessing heart failure outcomes (e.g. Krumholz, Circulation) specifically that could be considered. A more sophisticated administrative model might reduce some of the discrepancies seen. 2) The crude mortality is not significantly different but only becomes significant after multivariable adjustment. Do we know that patients in urban areas are truly more sick or is this a function of better capturing of comorbidities for patients residing in urban areas? Do the results persist if one stratifies by Aboriginal status and/or SES? It seems paradoxical that HF patients in urban areas would be more sick in terms of comorbidities. 3) A major limitation of the paper is that there is no information available on medications to potentially explain the differences nor is there information on access to care before or after the index hospitalization. As a result, it is not clear how a policy maker or clinician could act upon the results, nor what the implications might be readers living outside the area. The authors should make an effort to try and link their databases to drug or physicain claims databases which might exist in their area. 4) The importance of this paper for non-Australian readers needs more justification. Linked HF databases of this nature exist and have been published on in several other countries.

REVIEWER	Prof Robyn a Clark Flinders University Australia
REVIEW RETURNED	06-Mar-2014

GENERAL COMMENTS	Another excellent paper from this author and her group building upon previous linked adata analysis. A comment should be made about being cautious to make generalisations for the outcomes noted in these large heterogenious geogrphical areas.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1, Professor Warren Laskey

Response: For ease of reference, the responses are provided in parts, to address specific points raised by Reviewer #1, Professor Laskey. The points have been boxed up and responses to each provided accordingly.

We prefer titles that frame the research question and the study design rather than providing 'headlines'.

Response: The title could be revised to the following, if desired:

"Rural-urban differentials in 30-day and 1-year mortality following first-ever heart failure hospitalisation in Western Australia: A population-based study using data linkage

Although the urban-rural disparity of outcome has been previously described, I wonder whether there is more useful information here. The authors have collapsed 5 distinct geographic regions into 2

(rural, urban) with a resultant loss of variance for the variable "place". Since the 5 regions represent geographic clusters, the data need to be adjusted for the correlation of outcomes within clusters, In other words, perhaps a hierarchical approach is more appropriate here and perhaps the 95% CIs, when appropriately adjusted, might then include 1.0.

Response:

In the paper, five geographical regions were collapsed into two (metropolitan, rural) based on greater Perth metropolitan city definition for main results reported. The small case numbers in some of the rural sub-categories was a concern. Before deciding on this dichotomisation, a range of analyses were undertaken to investigate the effect of different categorisation of rurality on the research question.

1. A risk-adjusted analysis restricted to only rural patients showed no significant differences for 30-day mortality across all four rural subgroups (with the Inner regional patients as the reference group), hence justifying collapsing the subgroups into one rural group. This was despite an analysis using all five geographical regions in the risk-adjusted model finding that outer regional and very remote patients had increased odds of 30-day mortality [OR 1.30 (95% CI 1.03-1.63) and OR 1.46 (95% CI 1.02-2.10) compared to the Major city residents as the referent.
2. A sensitivity analysis was done and reported in the paper (Table 3) using 3 geographical categories (metropolitan, regional, and remote/very remote). Due to cell sizes the slightly higher OR for 30-day mortality in remote patients (1.29; 95% CI 0.98-1.69) did not reach significance in the fully adjusted model, and the adjusted HR for one-year mortality was not higher in remote patients. On this basis it was decided to report the main result based on the dichotomised variable but to include the results for the alternative categorisation as well.

In response to the specific recommendation made by Reviewer #1, an analysis was undertaken to examine potential correlation of outcomes within clusters, with the use of postcode as the cluster. In the fully-adjusted model (including the metro/rural covariate), addition of the variable – "postcode cluster" had no significant effect on 30-day or 1-year mortality (in 30-day survivors).

Additionally, the Metro/rural estimate changed only marginally from those reported in Table 2

We have made reference to this in the methodology section (page 9), with the main results reporting the model without clusters.

I am struck by how little the addition of covariates beyond age, sex, period add to the strength of the association. The 95% CIs overlap despite the numerical increase in the point estimates. Did tests for additional information (AIC, BIC, likelihood ratio) substantiate significant differences beyond the first model?

Response: For those who are not familiar with the Australian context, in particular, the remote/very remote areas, the following information is central to the design and statistical adjustments in the study.

About 54% of the Very Remote patients are Aboriginal patients with a mean age of 53.2 years vs 70.8 years (metropolitan patients). This suggests that rurality should be tested with and without Aboriginality in the risk-adjusted model. Our findings (see models in Table 2) indicated that rurality is still an independent predictor of outcome after adjustment for Aboriginality.

As to the strength of association beyond age, sex and period:

We have now revised the models (in Table 2), including Model 1 which adjusts for only age, then Model 2 to cover all socio-demographic variables, and step-wise hierarchical models in Table 2 (page 20).

- With age adjustment only, the age-adjusted odds ratio (OR) for 30-day mortality was 1.16 (95 % CI 1.01-1.33), 'c' statistic for area under ROC curve =0.616.

- With adjustment for socio-demographic variables (Model 2), the adjusted OR for 30-day mortality in rural patients was 1.18 (95% CI 1.01-1.38).'c' statistic for area under ROC curve =0.626.
- In the step-wise adjustment using Model 3 (socio-demographics, emergency presentation and the Charlson comorbidity index), the OR showed another level of change, increasing to 1.26 (95% CI 1.07-1.49), with 'c' statistic increasing to 0.690.
- Further step-wise adjustment to include individual comorbidities and revascularisation did not change the odds ratios much, beyond Model 3. However, the model fit improved with the 'c' statistic increasing to 0.714 (for Model 5), which is significantly better than the model (adjusted for age, gender and period, 'c' statistic = 0.618).

Similar changes were made for 1-year mortality (in 30-day survivors) –Table 2 (page 20). In summary, differences in socio-demographics and comorbidity burden between the rural versus metropolitan patients contributed significantly in addition to age, gender and period to the multivariate predictive model for outcomes.

The amendments have been made to the text (page 10 and Table 2). Additional tests (AIC, BIC) were repeated but not relevant.

Reviewer #2, Professor Jack Tu

This paper compared the outcomes of heart failure patients hospitalized in Western Australia using a linked administrative data set between those from urban and rural areas. The primary conclusion is that the survival is worse for those who live in rural areas, after adjustment for available confounding variables. The paper is generally clearly written. The major limitation of the paper is that the authors do not appear to have any additional information to help explain the disparities in outcomes exists.

Response: For our study, we have used the validated and near complete ascertainment of Western Australian linked Hospital Morbidity Data Collection (HMDC), linked to the Death Registry, to examine differences in the outcomes of interest (i.e. 30-day mortality and 1-year mortality in 30-day survivors) following index hospitalisation for heart failure between rural and metropolitan patients. To further strengthen our findings and explain why disparities exist, we have now included additional information to demonstrate the disparities in profiles of care between the metropolitan versus rural patients with/following first heart failure admission. Disparities in access to health services are well-documented for rural populations worldwide, and in Australia in particular[1]:

- ***Source of referral – Professional*** (Table 1, page 17-18) obtained from the HMDC, which showed that a significantly higher proportion of metropolitan (versus rural) patients were managed by specialist clinicians (25.2% vs 15.1%), while a higher proportion of rural patients were cared by GPs (18.4% vs 4.9%) prior to the index hospitalisation for heart failure.

- ***Mode of transportation*** *(*Table 1, page 18*).* Pre-hospital coverage by emergency medical service (ambulance) in rural areas is poorer. Our study cohort presented with index HF hospitalisations, about 93 % of which were emergency admissions. Metropolitan (versus rural) patients were more likely to be transported by the emergency medical service (EMS) by ambulance to the hospitals (38.5% versus 19.4%). By contrast, 65% of rural patients went to the hospitals via public/private transportation, suggesting that access to pre-hospital EMS(as an indicator of access to services) in the rural areas was inferior to that in the metropolitan areas and has been well-documented.

A paragraph on profile of care has been added on page 9 of the manuscript.

- ***The Emergency Department Data Collection (EDDC)*** has also been used to examine re-presentations to Emergency Departments (ED) within 1-year of follow-up from index admission for HF. Rural (versus metropolitan) patients had higher re-presentations (for any condition) to ED (mean 4.9±SD 5.7 versus 2.8±3.1, p <0.001), with 49.1% of rural ED presentations (versus 20.4% metropolitan had tri-age scores of 4 or 5 (semi or non-urgent cases). These findings suggest EDs are being used to fill the gaps in primary health care service provision or specialist services for rural patients, in contrast to the metropolitan counterparts. This additional information has been added to Table 1 and the text to pages 6 (methodology), 9 (results) and 13 (discussion).

Therefore, with 74% of rural patients being managed in rural regional and small district hospitals, it is likely that the type of care received from these hospitals and the rural primary care providers would have a differential impact on mortality, and particularly post-discharge outcomes.

We now specifically address other comments made by Reviewer #2.

1. *The authors used the Charlson index as their measure of comorbidity severity. There are more sophisticated administrative models available for assessing heart failure outcomes (e.g. Krumholz, Circulation) specifically that could be considered.*

A more sophisticated administrative model might reduce some of the discrepancies seen.

Response: The model by Krumholz et al, Circulation 2006, used an administrative claims-based model that was tested for performance against a medical record model based on 30-day mortality rates only. We examined 30-day and 1-year mortality (in 30-day survivors) following index hospitalisation for HF in our study. The authors re-analysed the data using a variation of the administrative model by Krumholz et al[2] for assessing 30-day mortality as recommended. The Krumholz's model was not largely different from the risk-adjusted model that we used initially, as many of the comorbidities listed in the Krumholz's model were the same as listed in the Charlson's comorbidities and others we used.

In addition to the Krumholz's model used in the re-analysis, we added other variables which have contextual importance [e.g. Aboriginality, socio-economic status (SEIFA and private insurance status), rheumatic heart disease, atrial fibrillation], with and without the weighted Charlson comorbidity index. Total comorbidity burden, apart from individual comorbidities, was found to be one of the strongest independent predictors of mortality in heart failure from the literature search. The 'c' statistic (area under the ROC curve) for the variation of Krumholz's model was found to be 0.656. The corresponding 'c' statistic for our model (with the inclusion of the Charlson comorbidity index and individual comorbidities) was 0.714, respectively, suggesting that our risk-adjusted model has a better fit. This suggests that our model is appropriate for in the Australian context.

Amendments to include this aspect has been included on page 10, last paragraph:

"The addition of the weighted Charlson index to the 30-day model using a variation of the administrative claims model[2] improved the 'c' statistic (under the ROC curve) from 0.656 to 0.714." Additionally, the covariates entered into the models are provided in the footnotes to Tables 2 and 3.

2. *The crude mortality is not significantly different but only becomes significant after multivariable adjustment. Do we know that patients in urban areas are truly more sick or is this a function of better capturing of comorbidities for patients residing in urban areas? Do the results persist if one stratifies by Aboriginal status and/or SES? It seems paradoxical that HF patients in urban areas would be more sick in terms of comorbidities.*

Response: Few sub-points are listed in 2. For ease of reference, we will address it separately:

a) The crude mortality is not significantly different but only becomes significant after multivariable adjustment

Response:

The significant difference in age between rural and metro groups is the main reason for similarities in crude but not adjusted mortality (see Table 1).This was shown when the association of rural residence with mortality became significant, solely on age adjustment alone [OR 30-day mortality for rural patients was 1.15 (95% CI 1.01-1.33, p=0.035)]. Aboriginal patients who constituted 54% of very remote patients, had a mean age of only 53.2±14.8 years (versus 70.8 years±11.7 years metropolitan patients). The younger population profile of patients with manifest cardiovascular disease in rural areas is a well-established fact[1]

Model 1 in Table 2 has been changed to include all socio-demographic variables. Other models show a step-wise hierarchical adjustment for emergency presentation, Charlson index, then individual comorbidities and interventions (PCI/CABG). Despite the adjustments, rurality was consistently associated with higher odds/hazard of death.

b) Do we know that patients in urban areas are truly more sick or is this a function of better capturing of comorbidities for patients residing in urban areas?

Response:

A large majority (about 95%) of the both metropolitan and rural HF patients would be quite sick on presentation as they were emergency presentations and there is generally a high threshold for hospital admission. Crude comorbidity prevalence of HF patients in urban areas is higher primarily because they are significantly older than rural patients; age-specific comorbidity prevalence is not. For example, Aboriginal patients (the majority of whom reside in rural locations) have been widely reported to have a heavier comorbidity burden, despite being much younger. Moreover, the Western Australia Department of Health has a well-established quality assurance program in place, which includes regular checks on coding by clinical coders throughout WA. Additionally, co-morbidities for rural patients would be based on 5-year histories which would include admissions to urban and rural hospitals alike.

c) Do the results persist if one stratifies by Aboriginal status and/or SES?

We had recently published another study in the International Journal of Cardiology, entitled "Incidence of first heart failure hospitalization and mortality in Aboriginal and non-Aboriginal patients in Western Australia, 2000-2009". In that study, we found rural residence remained a significant predictor of mortality in the fully adjusted model (for older (≥ 55 years) patients and the whole cohort), reinforcing the fact that access to health care services in rural/remote areas is a key issue leading to poorer outcomes in Aboriginal Australians.

No significant interaction between geographic regions and Aboriginality was found. After stratification and restriction to only non-Aboriginal patients (as suggested), the risk-adjusted models consistently showed a strong association of rurality with worse outcomes for rural patients. This suggests that Aboriginality should be included as a covariate in our modelling.

In rural areas SEIFA, an area-based SES indicator, does not discriminate well for SES due to heterogeneity in rural locations. However, adjustment was made for SES with two variables – SEIFA and private insurance status (as proxy for SES).

d) It seems paradoxical that HF patients in urban areas would be more sick in terms of comorbidities.

As indicated above, metropolitan patients have more comorbidities overall because they are significantly older than rural patients. However, it is widely reported that Aboriginal people have more comorbidities than non-Aboriginal people despite their younger age profile. The same had been reported in our recent study published in International Journal of Cardiology.[3] Diabetes, renal failure, COPD and are more common in hospitalised HF patients from the rural areas.

Apart from comorbidities, our findings showed that despite the older age profile of urban patients, the level of post-discharge care in the metropolitan areas is likely better compared to rural areas, contributing to the disparity in the outcomes examined. This is further supported by the primary referral source and the ED re-presentations in metropolitan versus rural patients (in Table 1).

3) A major limitation of the paper is that there is no information available on medications to potentially explain the differences nor is there information on access to care before or after the index hospitalization. As a result, it is not clear how a policy maker or clinician could act upon the results,

nor what the implications might be readers living outside the area. The authors should make an effort to try and link their databases to drug or physicians claims databases which might exist in their area.

We lack medications data for our cohort and this was a limitation stated in our paper. However, in a separate study undertaken by our team (ref: Gausia et al[4])'s paper), the authors found adjusted evidence-based prescription at discharge for patients with acute coronary syndrome was significantly lower in district hospitals versus metropolitan teaching hospitals (OR 0.51, 95% CI 0.32-0.82), as well also in patients with regional versus metropolitan residence (OR 0.55, 95% CI 0.39-0.77). This finding is also likely applicable to the uptake and adherence to evidence-based therapy for HF patients discharged from non-tertiary and rural care hospitals. We have previously shown that the discharge prescription of evidence-based HF medications had a significant impact on subsequent survival.[5]

4) The importance of this paper for non-Australian readers needs more justification. Linked HF databases of this nature exist and have been published on in several other countries.

The problem of inequalities in health burden and access to health care related to rurality and remoteness is a common theme across many countries including high socioeconomic countries such as Australia and Canada. It is therefore an important issue that is relevant to health policy, health service delivery and health care planning in many countries beyond the local context.

This paragraph has been added to the manuscript (pages 14-15).

Reviewer # 3, Prof Robyn a Clark

Another excellent paper from this author and her group building upon previous linked data analysis. A comment should be made about being cautious to make generalisations for the outcomes noted in these large heterogeneous geographical areas.

Response: We thank Reviewer #3, Professor Clark for her comments. We are very mindful of the heterogeneity with Aboriginal people commonly residing in the Very Remote regions. Our findings were based on fairly robust models, with risk-adjustments made for several contextual factors, including Aboriginality, socio-economic status (with SEIFA and private insurance status as proxies) and other factors/comorbidities listed in Table 1. Earlier stratified analyses had also been undertaken and the results consistently show rurality being an independent predictor of worse outcomes in this cohort of index heart failure patients.

A comment has been added to the manuscript to highlight the heterogeneity in geographical areas on page 13:

"The heterogeneity in the different geographical areas needs to be highlighted."

Thank you.

Yours sincerely

Tiew-Hwa Katherine Teng (on behalf of all the co-authors)

Research Fellow

Combined Universities Centre for Rural Health, University of Western Australia

References

1. Australian Institute of Health and Welfare. Rural, regional and remote health - Indicators of health: Canberra, AIHW; 2005.
2. Krumholz HM, Wang Y, Mattera JA et al. An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with heart failure. *Circulation*. 2006; **113**:1693-701.
3. Teng TH, Katzenellenbogen JM, Thompson SC et al. Incidence of first heart failure hospitalization and outcomes in Aboriginal and non-Aboriginal patients in Western Australia, 2000-2009. *Int J Cardiol (In-press)*. 2013.
4. Gausia K, et al. Evidence-based prescribing of drugs for secondary prevention of acute coronary syndrome in Aboriginal and non-Aboriginal patients admitted to Western Australian hospitals. *Internal Medicine Journal*. 2014; **in-press**.

VERSION 2 – REVIEW

REVIEWER	Warren Laskey MD University of New Mexico, USA
REVIEW RETURNED	01-Apr-2014

GENERAL COMMENTS	authors have satisfactorily addressed concerns and questions and revised the paper accordingly

REVIEWER	Jack Tu ICES, University of Toronto Canada
REVIEW RETURNED	09-Apr-2014

GENERAL COMMENTS	I am satisfied with the quality of the authors responses to my original review.