Author’s response to reviews

Title: Spatial variation in the management and outcomes of acute coronary syndrome

Authors:

Alain Vanasse (alain.vanasse@usherbrooke.ca)
Theophile Niyonsenga (theophile.niyonsenga@chus.qc.ca)
Josiane Courteau (josiane.courteau@chus.qc.ca)
Jean-Pierre Gregoire (jeau-pierre.gregoire@pha.ulaval.ca)
Abbas Hemiari (abbas.hemiari@chus.qc.ca)
Julie Loslier (julieloslier@hotmail.com)
Goze B Benie (Goze.bertin.benie@usherbrooke.ca)

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Author’s response to reviews: see over
RESPONSES TO THE REVIEWER RICHARD GLAZIER:

Minor Essential Revisions

1. **Abstract and background**: a) *Acute coronary syndrome should be defined.*
   
   Acute coronary syndrome is defined in our study as myocardial infarction or unstable angina. This precision is now integrated in the text with corresponding ICD-9 codes.

2. **Abstract**: b) *The conclusion relating to the potential benefits of ICP in the management of ACS should be removed. This is a statement about effectiveness of an intervention which is much better made on the basis of randomized trials and not on the basis of associations found in administrative data.*

   We totally agree with this comment. We wrote the conclusion according to the objectives of the study.

3. **Methods**: a) *The method for calculating distance should be better specified. If it was based on straight-line distances or if it took the road network into account is not clear.*

   The distance from residence to the specialized cardiology center was measured by the aerial distance (straight-line). This is now specified in the revised manuscript.

4. **Methods**: b) *The terms ‘specialized cardiology center’ and ‘tertiary cardiology center’ should be defined and the way they were identified described.*

   These two expressions referred to the same type of center. We now use ‘specialized cardiology center’ throughout the text. These 16 specialized centers were identified via the Quebec tertiary cardiology network website.

5. **Methods**: c) *It is not clear why 4 groups were chosen for Hierarchical Cluster Analysis. This choice should be explained. The notion of ‘distance’ could either be distance between variables values or it could be spatial distance of adjacency that was used. This is not clear and should be further explained.*

   Hierarchical cluster analysis is a method based on measures of similarities (or distance) between clusters computed from their values of one or several variables. This kind of distance has nothing to do with the spatial distance between coordinates. We acknowledge that this can be very confusing so we used instead of the word ‘distance’ the concept of ‘similarity’. The method is now better described in the text. The choice of the number of clusters is based on graphical analyses of the dendrograms produced by the method, the idea being to display a sufficient number of clusters in order to have homogeneous groups (intra-group homogeneity) dissimilar enough (inter-group heterogeneity). An example of dendrogram is presented in Figure 1.
6. **Methods:** d) The authors should explain why a 20% sample was used for the Monte Carlo significance test instead of the whole study population.

   A sample was necessary because of the very large population (over 25,000 patients) and the very time consuming execution of the GWR software particularly in the logistic regression models.

7. **Methods:** e) It is not clear whether GWR was used in the analysis or whether it was merely alluded to in the context of the Monte Carlo significance test. This should be clarified.

   The GWR method was in fact used. The Monte Carlo test was used only to test whether or not the GWR local parameters varied spatially. This is now clarified in the text.

8. **Results:** a) It is not clear if the regressions depicted in Figure 2 controlled for all of the factors presented in Figure 2. It is not clear if they controlled for sex and precocity. This should be clarified in the text and on the figure.

   As also suggested by Dr. Nallamothu, the regressions are now presented in a table instead of a figure. All odds ratios and ratios between means are adjusted for all the other covariables and this is now clearly stated.

9. **Results:** b) The spatial clustering of residuals indicates geographic autocorrelation that is not accounted for in the model. This can affect the accuracy of regression parameters and variance estimates. Do the authors feel that the magnitude of this effect warrants a correction such as use of spatial autoregressive modeling? Please explain why or why not.

   We agree with the reviewer’s comments. Indeed, the global model residuals show spatial autocorrelation. As Fotheringham et al (2002) pointed out; allowing geographically varying relationships to be modeled through spatially varying parameter estimates removes much of the problem of spatially autocorrelated errors (residuals). This is what was done in the regression models presented in this paper in which GWR is used as an alternative solution to spatial dependency.

10. **Discussion:** a) The paradoxical finding of decreased length of stay with proximity of cardiology center but increased length of stay with invasive cardiac procedure (where proximity and procedures are associated) should be further discussed.

    The paradoxical finding of decreased LoS with proximity to specialized cardiology center with finding of increased LoS with ICP and increased likelihood of ICP with proximity can be explained by the interaction between ICP and proximity to cardiology center in the evaluation of LoS. Secondary analyses (table 3) show that, for patients with ICP, the LoS is lower for patients near a cardiology center than for those farther, whereas, for patients not receiving ICP, those that are closer have not a lower LoS than the others. We can also argue that patients living
far from a specialized cardiology center will stay longer at the hospital during the whole episode of care if they received an ICP because of hospital transfer from non-specialized to a specialized cardiology center. These comments have been included in the discussion.

11. Discussion: b) The province of Quebec is referred as a country but is a province.
We corrected this in the text.

**Discretionary Revisions**

12. Methods: a) Given an expected skew in data distribution, length of stay could also be reported as a median time.

This is a fact that the length of stay distribution is much skewed. This is why we used a log-transformation in the model. The median gives us complementary information and we added this information in the Table 1.

13. Results: It would be very useful to have the analysis repeated using different distance buffers such as 35 km, 50km, and 100 km. As this would require considerable additional analysis, I consider it to be a suggestion left to the authors’ discretion.

This is indeed a very good suggestion and we did the analyses with a category variable with cut points of 32, 64 and 105 km. We chose these cut points based on studies (Scott et al; Winters et al) that reported transportation time of respectively 60, 90 and 120 minutes to cover a distance of 32, 64 and 105 km.

**RESPONSES TO THE REVIEWER BRAHMAJEE NALLAMOTHU:**

**Major Compulsory Revisions**

1. Outcomes evaluated. Did the authors consider evaluating outcomes related to death such as in-hospital death and 30-days mortality rates? It would be important to see whether death rates also vary across geographic regions and if this variation is due to spatially-related factors. Of course, the latter may be unavailable in the registry, but these outcomes are very meaningful. At the very least, the authors need to comment on why they did or did not evaluate death as a clinical outcome.

Indeed, death is a very important outcome. In-hospital mortality was available so we included this new outcome in our analysis. Unfortunately, the 30-days mortality data was not available for the year 2001, so we could not have enough follow-up for all patients in the cohort. Also, for those with available data on death, only the year and the month was given because of confidentiality concerns. This can be a problem when considering a 30 days delay between discharge and event. Moreover, a secondary analysis shows that approximately 1% of the cohort
would have died from a coronary disease within 30 days from the index hospitalization.

The focus of the paper is more on management care than health outcomes like mortality or morbidity. The manuscript now reflects better this perspective.

2. Additional covariates in model and residuals confounding. I am concerned that the multivariate models, which primarily adjusted for age and gender, have a substantial amount of residual confounding that needs to be addressed. One problem might have been that age was only modestly adjusted for using a dichotomous category. Geographic proximity was only evaluated using a dichotomous category in the models that included it. Were other potential relationships between age or distance and clinical outcomes explored? It is easy to imagine that an individual who live only 1 km from a cardiovascular center may be considerably different from someone living 30 kilometres away.

We agree with the reviewer and we redefined the variable distance to a specialized cardiology center in several categories with cut points of 32, 64 and 105 km. We chose these cut points based on studies (Scott et al; Winters et al) that reported transportation time of respectively 60, 90 and 120 minutes to cover a distance of 32, 64 and 105 km. Regarding age, we used this variable as continuous in the regression models but we described the outcomes by suggested age category (<55, 55-64, 65-74, 75-84, ≥85).

Also, a number of additional factors that can impact on these clinical outcomes were not adjusted for at all in the multivariate models. These include co-morbidities (which may be limited by the use of administrative data) and urgency of admission. The fact that urgent readmissions cannot be differentiated from elective readmissions is a particularly major concern. High early readmission rates in the remote regions may simply have been due to discharge after stabilization at a remote hospital and then elective readmission at a specialized cardiology center two weeks later for a scheduled procedure like coronary angiography. This would be very appropriate. The authors seem to recognize this limitation in their discussion, but that does not prevent it from being a major obstacle to interpreting their findings. Finally, socioeconomic variables, such as the median income levels for the ZIP code, may be available by linking to census information and could provide additional insights. The authors should comment on their inclusion or exclusion of these factors.

Indeed, differences observed in early hospital readmission rates probably reflect more the difference in the managed cares than in health outcomes like morbidity. As raised by the reviewer, elevated rates in some regions may have been due to discharge after stabilization and then elective readmission at a specialized cardiology center for an ICP. The regional disparities observed may well represent
an adaptation of the health care system for geographical disparities in order to deliver good quality of care. To test this hypothesis, it would require a very complex research design, using qualitative and quantitative analyses. Such studies would have to take into account determinants of care at many levels such as: at the sociological, cultural, political, and economical level, as well as at the professional and geographical level. This was added in the discussion section.

3. **Policy impact.** The authors describe a substantial amount of spatial variation in the three clinical outcomes. But geographic variation in utilization and outcomes has been well-described before in other geographic regions. It is therefore not surprising, and it may not be the most important contribution of this manuscript (although the authors may argue differently). I believe the manuscript’s ability to comment on the relationship between spatial issues like the importance of proximity to a specialized cardiology center to outcomes is inherently more interesting from a policy perspective. However, the ability to do so is substantially limited due to residual confounding. I am unclear as to what their message should be: do their findings support opening up additional specialized cardiology centers? Or perhaps better systems for centralizing care at existing centers are needed? The authors should comment on the policy implications, if any, of their findings to expand its interest to a larger audience.

As highlighted by this study, regional disparities in the province of Quebec may well represent an adaptation of the health care system for geographical disparities in order to deliver good quality of care, despite major limitations in terms of physical accessibility to specialized cardiology centers. In terms of policy impact, it could also mean that regional based decision making may provide valuable contribution in the management of care for ACS, taking into account the limited physical accessibility of specialized cardiology centers.

*Minor Essential Revisions*

1. **Was the 35km catchment area obtained using ‘as the crow flies’ distances or road network distances?**

   The distance from residence to the specialized cardiology center was measured by the aerial distance (straight-line). This is now specified in the revised manuscript.

2. **The authors should describe exactly how they calculated their standardized rates for ICP and early readmission. I’m assuming that they simply compared observed to expected rates of events to create standardized ratios. If so, they should state this directly and avoid using the term ‘SMR’ since it refers specifically to standardized mortality ratios and is little confusing.**
The standardized ratio was indeed the ratio between observed number and expected number given age and sex. We eliminate the term SMR and replace it by standardized ratio throughout the text.

3. **Could the authors expand on hierarchical agglomeration and why it is superior to the other methods that were noted to ‘bring in the notion of distance’?**

Hierarchical cluster analysis is a method based on measures of similarities (or distance) between clusters computed from their values for one or several variables. This kind of distance has nothing to do with the spatial distance between coordinates. We acknowledge that this can be very confusing so we used instead of the word ‘distance’ the concept of ‘similarity’. The method is now better described in the text. The choice of the number of clusters is based on graphical analyses of the dendrograms produced by the method, the idea being to display a sufficient number of clusters in order to have homogeneous groups dissimilar enough. An example of dendrogram is presented in Figure 1.

4. **The figure titles and legends use minor variations in terms: for example, early readmission is alternatively referred to as readmission and EHR and ICP is referred to as PCI.**

This has been corrected on the new maps.

**Discretionary Revisions**

1. **The geographically weighted regression (GWR) analysis shows evidence of spatial non-stationarity for key coefficients in the multivariate analyses of LoS and early readmission. Did the authors map out differences in local estimates of these coefficients and were any geographic patterns noted?**

   A trend analysis of the parameter estimates shows that an increased relationship between ICP and LoS is observed as we move away from Montreal and the city of Gatineau in Outaouais, but no clear trend is observed in the local relationships between distance to a specialized cardiology center and LoS. We added a figure to show this trend.

2. **I would eliminate the use of the abbreviation ER – it overlaps too much with the concept of emergency room. These were early readmissions and it is unclear if they were urgent or elective.**

   We eliminate the abbreviation ER and replace it by EHR for early hospital readmission.

3. **Figure 2 may be better represented using a table.**

   All regression analyses are now better presented in a table.