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Title	**Geographic clustering of emergency department presentations for acute coronary syndromes and heart failure in Alberta, Canada: a population-based study**
Authors	Rhonda J. Rosychuk PhD, Brian H. Rowe MD MSc, Finlay A. McAlister MD,MSc
Reviewer 1	Dr. Mohamad Anas Hussain,
Institution	Department of Surgery, University of Toronto, Toronto, Ont.
General comments (author response in bold)	1. What is the accuracy of ACS and HF diagnostic codes? Are there any validation studies that have examined this? **Response: We did not complete a validation component to this study. In general, when examined, these Alberta databases have been found to be accurate for ACS and HF (Tonelli et al. 2015). We have made a comment to this effect in the Limitations section.** 2. How you determined comorbidities is somewhat unclear. I understand 2+ physician claims were required to capture ACS and HF within 2 years, but it's not clear if these were outpatient visits or hospitalizations. Furthermore, details on how you captured other comorbidites (COPD, diabetes, etc.) are required (i.e. diagnosis codes used; their accuracies; were these again outpatient, inpatient, or both?). **Response: The physician claims were mainly outpatient visits. The extraction from the Physician Claims File included a facility type variable. The categories for this variable include active treatment hospital (including active treatment clinic) and practitioner's office. For ACS, 40% of physician claims in the prior 2 years were categorized as active treatment hospital and 50% were at a practitioner's clinic. For HF, 48% of physician claims in the prior 2 years were categorized as active treatment hospital and 41% were at a practitioner's clinic. As we cannot separate hospitalizations vs clinics, we are unable to identify which of the physician claims relate to hospitalizations. The comorbidities were based on the Deyo ICD-9-CM coding scheme. That coding scheme specifies the ICD codes to use for each comorbidity.** 3. Can you please state what each cluster represents more clearly in the methods section. Does the primary cluster represent geographical areas with populations at highest unadjusted risk for ER visit? Followed by cluster 2 and 3? I wasn't able to establish this from the paper. **Response: The spatial scan considers all possible combinations of neighbouring areas that have less than the specified proportion of population (<50% of the Alberta population in our case). For each of the combinations, the likelihood ratio is calculated and compares the risk (for having an ED visit) inside and outside the combination relative to the risk for the entire region. We have clarified this aspect in the Methods section.** 4. Why enter prior ED history of ACS or HF in the multivariable models but not enter prior hospitalization for ACS or HF? **Response: Our data extraction did not include diagnosis for the hospitalization. Patients may have been admitted through the ED and may have been captured in the prior ED history variable. In addition, the extraction from the Physician Claims File included a facility type variable. The categories for this variable include active treatment hospital (including active treatment clinic) and practitioner's office. Hence, the prior history of physician claims variables may also include diagnoses in hospital. We do recognize that the lack of diagnosis for the hospitalization data is a limitation and had included this aspect in the discussion of limitations.** 5. Please report in text or flow diagram why ~700 ACS and ~450 HF patients were excluded from the analysis. **Response: We did not exclude ~700 ACS and ~450 HF patients from the analyses. We are unclear where the figures quoted are originating. We only excluded 2 patients who did not have area data, the key requirement for the spatial scan test. Our data extraction included 13,283 ED presentations for ACS (7,059) and HF (6,224). Because some patients had more than one ED presentation and the unit of analysis is unique patients, our analyses are based 6,342 ACS and 4,780 HF patients. We have included a flow diagram for clarity.** 6. Is there a way to report the geographic variation of the overall population of Alberta (in a map or including a rural versus urban variable)? It would be helpful for the reader to understand the locations of rural and urban communities in Alberta this can then be compared (even visually) with your ACS and HF cluster maps to support (or oppose) your findings of lower specialty physician visits and higher ER visits among potentially rural/low resource communities. **Response: There are many sources of maps with population density and community locations for the interested reader (e.g., https://commons.wikimedia.org/wiki/File:Alberta_Census_divisions_-_population_density.svg, https://www.citypopulation.de/Canada-Alberta.html). We are reluctant to include a population map for Alberta in our manuscript because spatial scan adjusts for the underlying population and the clusters are not identified because of low population but because the risk is statistically significantly higher inside the clusters than outside the clusters. Visually comparing the cluster results and the population density map could potentially confuse readers.** 7. The discussion can be strengthened by discussing potential policy implications of these data. **Response: We have briefly mentioned the possible policy applications.** 8. Figures: It would be helpful for the reader to label major cities (Calgary and Edmonton at minimum). I would also change the colours as it's difficult for the reader to appreciate the different shades of grey (2 of the colours actually look blue). **Response: Edmonton and Calgary have been provided as insets. We have provided labels on the insets to make that aspect more clear. We have revised the maps so that the shading is all greyscale.**
Reviewer 2	Dr. Corinne M. Hohl
Institution	Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute, Vancouver, BC
General comments (author response in bold)	Introduction: 1. Lines 16, onwards: I would think that this could also represent lifestyle/cultural, dietary or socioeconomic variations between areas, in addition to differences in disease severity, and healthcare access and delivery attributes. **Response: We had considered that differences in disease severity would capture the types of factors you suggest. We have addressed that aspect in the Interpretation section.** 2. Objectives: Your stated objective is to examine geographic variation in presentations made by adults (age ≥ 35 years) to EDs in the province of Alberta, Canada for ACS and HF during 2010/2011. However, you are dealing with administrative data. Thus, please modify

your objectives statement to be clear that you are interested in Canadians diagnosed with, and visits coded as or attributed to ACS and HF. (See my comment below about this issue in the Methods section).
Response: We have changed as per your suggestion.

Methods:
3. Has the accuracy (or inaccuracy) in the codes you used for case identification been evaluated? If so, please discuss this literature. Unfortunately, diagnostic procedural codes tend to be far less accurate than procedural codes, as physician billing is often based on the latter. So, the clinical uncertainty in these types of diagnoses (e.g., in patients presenting with shortness of breath), tends not only to be mirrored in the diagnostic coding, but may be amplified by additional inaccuracy in coding. Please discuss this in your methods, if the codes you used have been validated. If not, this must be discussed in a discussion/limitations section.
Response: Please see response #1 to Reviewer #1.

4. Is there any geographic variation in coding by region in Alberta? If there is (or could be) variation by hospital, please discuss. If there could have been any variability in the manner in which these diagnoses are coded by geographic region/hospital, any findings of differences in disease distribution could be related to this. I suggest including the hospital where the patient presented in your analysis to account for this possibility.
Response: While we have not examined this in particular, we should not have geographic variation in coding because trained nosologists are completing the coding (even in the ED), and a network of surveillance and education exists across the province. We do not have a hospital identification number in our extracted data set, so we are unable to include hospital in our modelling. Most areas only have one hospital so the variation among hospitals is not expected to be great, within the same area.

5. Line 57: Why not use postal codes? The first three digits of the postal code can be used for this without the risk of de-identifying data, and would provide richer socioeconomic data than eligibility for welfare. If you cannot use them, please discuss this in your limitations section.
Response: The sub-regional health authorities (now just simply called areas in the revised manuscript) provide well-circumscribed areas within each of the five Health Zones in Alberta from which to draw conclusions; they allow for the calculation of stable rates (Ellehoj E, Schopflocher D. Calculating small area analysis: Definition of sub-regional geographic units in Alberta. Edmonton, AB: Alberta Health and Wellness; 2003) and results are relevant for decision-makers working in the Health Zones. In our earliest discussion with Alberta Health on geographic analyses, the recommendation was to use the sub-regional health authorities as the geographic units rather than postal code areas. We have made a comment in the Limitations section.

6. Diagnostic codes: Why did you not supplement your search by using procedural codes for PCI and other cardiac procedures? These codes have high diagnostic accuracy.
Response: The intervention code is not a mandatory field and many ED presentations do not have any interventions reported. In addition, reliable data on PCI is maintained within another data base (APPROACH). We also wanted to keep the data extraction relatively simple based on mandatory fields.

7. Control for confounding: You chose several chronic disease states to control for confounding. However, the predisposing factors for ACS and HF are not identical. Particularly for HF, there are many other predisposing conditions that might have been useful to control for (e.g., alcohol abuse, valvular heart disease). Can you elaborate why you chose the ones you did, and how omission of others may have influenced your analysis and results?
Response: We used the Charlson Comorbidity Index (described in Physician Claims part of the Methods section) to capture key predisposing conditions like valvular heart disease. In addition, we included chronic obstructive pulmonary disease, diabetes, hypertension, and kidney disease as separate predisposing conditions in our models because we felt that these were the most likely conditions that were important for outcomes and had relatively high frequencies in our dataset. We do not think we have missed a major predisposing condition that would greatly influence our results (note that factors like alcohol abuse are not accurately captured in administrative data).

Results:
8. Table 2 requires more explanation in its title or legend.
Response: We have improved the caption.

9. It is not quite clear to me in generating the clusters what was regarded as the reference. I am unfamiliar with this type of geographic special analysis. An explanation in the methods would be helpful.
Response: The reference would be the rate in the entire geographic region. Please see comments to Reviewer #1 Item #3 for further information.

Discussion:
10. Lines 2939: see my comments above. I'd argue that other factors need to be considered, and that only some risk factors for both overlap. This seems to me to be a rural urban split, and while there are differences between clusters, that split is the most striking to me.
Response: In North America the majority of HF is on the basis of coronary disease, so there are common risk factors for ACS and HF. The major risk factors for non-coronary disease HF are hypertension and DM, which are included in the Charlson index. We note that administrative data do not have all potential factors recorded so not all factors can be included in an analysis. As for rural/urban, it is not just solely the situation that rural areas have more patients presenting. If that were the case, then many more rural areas would have been identified as parts of clusters.

11. Lines 37, and beyond: "This result suggests that access to specialists may be reduced in some areas and gives rise to the hypothesis that earlier specialist intervention may reduce future ED presentations" If you feel that lifestyle (e.g., obesity rates, physical activity levels) and differences in disease distribution do not explain your results you could test this hypothesis. Specialists modify health in two main ways: (1) using procedures (e.g., PCI for ACS), and (2) using pharmacotherapy. So, your argument would be greatly strengthened if you could add healthcare management attributes to your analysis by looking at:
a. procedural codes related to ACS
b. medication use claims data for key medications for each condition.

	Response: There are 10 intervention fields in the database that are coded according to the Canadian Classification of Health Interventions. Our data extraction included these 10 fields and approximately 27% of the ED presentations for each condition are blank. It is unclear if the blank means that no interventions took place or if interventions took place and were not reported. Based on this uncertainty, we did not pursue analyses that included interventions. In addition, the intervention fields in the database do not include medications, so analyses by medication are not possible. 12. Please elaborate how your study results should be interpreted and used by health policy makers, if you feel that is warranted. What are the practical implications? **Response: Please see response #7 to Reviewer #1.**
Reviewer 3	Dr. Balthasar L Hug
Institution	Internal Medicine, Basel University Hospital, Basel, Switzerland
General comments (author response in bold)	Methods: 1. P. 6, line 30: The authors should explain in brief why they chose the age cutoff of 35 years for their patient population. Was it because of the dataset? What about young people suffering heart attacks from cocaine? A short explanation of the authors' thoughts should suffice. **Response: The dataset did not have such an age restriction and we made the decision to restrict the extraction of records to patients aged 35 years or older at the time of the ED presentation. We focused on patients ≥35 years of age because events in the younger age group may differ in cause (e.g., drug use, alcohol use, electrolyte imbalance, and exercise), as you have suggested, and are infrequent. We have further clarified this choice in the Methods section.** 2. P. 6/7, ICDcoding: on p. 6 we learn that the main diagnosis is based on ICD10CA in the MACAR database, while for the physician claims in the two prior years the ICD9CM was used. Here the reader has to question the comparability of the two ICD systems. How did the authors manage the incongruity of the two systems? There are lots of papers on this topic such as the one by Quan et al (2008) in Canada[Quan H, Li B, Saunders LD, et al. Assessing validity of ICD9CM and ICD10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res 2008;43(4):142441]. The authors should add a sentence or two on this topic to their paper about possible influences on their results. **Response: The diagnosis in MACAR is used to identify the cohort. The Physician Claims diagnoses were used to assess comorbidities for the patients identified in the cohort. Incongruity is not an issue here because different database diagnosis fields were used for different aspects of and purposes in the study. We have added the Quan et al. paper you bring up as well.** 3. Minor: p.7, line 21: there is a superflous „i" between the words „Diagnoses" and „are coded..". **Response: Corrected.** 4. P. 6, line 39: „Alberta had 70 subregional health authorities...in 2003." This expression is puzzling since the reader assumes that today it must be different. The next question is how was it in 2010/2011 when the study took place? According to the study the reader assumes it must have been the same as in 2003. Then why do the authors not write „Alberta has...."? They should clarify this sentence. **Response: We agree. We have removed the 2003 reference as it is not relevant and have made the explanation clearer.** 5. P. 7, first two lines: expressions like „First Nation individuals" and „First Nation bands" are unknown to non-Canadian readers. The authors should either explain these types of social security or use general terms well understood abroad. **Response: We have used the specific terminology from the Canadian government and have provided the reference for the terminology. These terms may not be specifically known by all readers and our strict word count (<2500 words) means we cannot elaborate on all aspects.** Results: 6. Figures 13: Abbreviation explanations should be added to all of the figures. **Response: These have been added.** 7. The naming of the clusters should be consistent throughout the paper. Expressions such as „the first secondary cluster" on line 43, p.10 are confusing; it is called „cluster 2" in figure 5 and should stay the same in the text. The reader is confronted with three types of clusters, the areas inside and outside the clusters and cluster merging (p. 10, first line). It helps to call them cluster 13, combination of cluster could be called „A", „B" or the like to assist the reader in understanding the clustering and/or draw a small figure about the clustering procedures. This is very important for the paper. **Response: We regret the confusion and have used more consistent labeling in the revision.** 8. Supplementary Table was not available to this reviewer; it should be made available. **Response: We thought that these were uploaded for the original submission and have verified they are there for the revision.** Interpretation: 9. Here the challenge is to explain why the two illnesses do not match geographically regarding clustering although the same two types of specialists are needed. Basically, reasons could be 1) different regional infrastructure, 2) different regulations to health access or 3) regionally different patient characteristics. It would help the interpretation of the results of this study enormously, if the authors would provide some more information on these three points as suggested below. In a second step the interpretations on p. 11 and 12 should be adapted and rewritten: a. Infrastructure: Here the authors do not tell us anything about the available specialists (internists & cardiologists) in a designated area: are there regional differences regarding specialist density that might explain these differences? **Response: Our data extract did not include specialist concentration by area and Alberta Health releases few physician details. We do know that Cardiologists and Respirologists are largely concentrated within the two major urban areas (e.g., Calgary/Edmonton), rarely in the regional centres and never in the smaller and remote centres. Certainly, more rural and remote locations would have even fewer**

	specialists "visiting" or providing tele-consultation. Specialist access would be the same for both conditions in a geographic area. Further, the same definitions and techniques were used for each of ACS and HF and any differences in results are not attributable to methodology. b. Regulations: Are there different regulations in these health areas that might influence health access for patients with ACS or HF? **Response: There are no differences in regulations among these health areas that might influence health access for patients with ACS or HF. All EDs in Alberta would follow the same regulations mandated by Alberta Health, however, like other provinces, practice variations likely occurs. That is why we have suggested that ED management may be the reason for geographic differences. This study may identify the results of practice variations. Further, the same definitions and techniques were used for each of ACS and HF and any differences in results are not attributable to methodology.** c. Patient characteristics: Are there areas of more or less privileged people living in certain of the studied areas? This will influence health care behavior in these areas or in other words: How are the socioeconomic proxies for the areas studied here? Are they all identical? **Response: Statistics Canada has produced a map of Canada (including Alberta) depicting median incomes in 2010 (https://www12.statcan.gc.ca/nhs-enm/2011/as-sa/map-carte/thematic_download-thematiques_telecharger_R3-eng.cfm?SERIES=11&GEOCODE=1). The clusters identified include a mix of areas that are above or below the national median. Many areas are too sparsely populated to be categorized. In our regression modelling, only the model for ACS included a statistically significant effect socio-economic proxy. Specifically, the areas identified as clusters for ACS were more likely to have subsidized adults and seniors present to the ED than the areas that were not identified as clusters. While this effect is statistically significant, it does not necessarily mean that the areas have less privileged people in the area. We only make this comment about the individuals presenting to the ED, not the general population. Further, the same definitions and techniques were used for each of ACS and HF and any differences in results are not attributable to methodology.** Conclusions: 10. These should be adapted according to the answers to the three questions in the „Interpretation" section. **Response: We have revised the conclusion section as follows:** **"In conclusion, this study showed geographic variations based on the number of people presenting to EDs for ACS or HF which was not entirely explained by differences in demographics or comorbidities. Patients in the high cluster areas did, however, exhibit lower rates of prior contact with specialist physicians. While there may be other potential differences that may contribute to the clustering (e.g., cultural, dietary, environmental), these were not possible to explore in these analyses. We hypothesize, however, that increasing specialist access may reduce the reliance on ED services in high cluster areas, although this is a hypothesis that should be tested empirically. Innovative interventions to improve access (e.g., tele-consultation, remote monitoring, specialist visiting clinics in regional centres) need to be explored."** Acknowledgements: 11. Are there no persons to thank for their help for this publication? I am positive that there are at least some. **Response: We have acknowledged Alberta Health for their contributions as they wish to be acknowledged. All analyses were conducted by Dr. Rosychuk. She had an assistant execute her code and her data files for the spatial scan on the assistant's computer because it had SatScan installed. The assistant did not participate in the choice of analysis or interpretation of results, and thus was not listed in the acknowledgments. Most of the funders are mentioned in the Acknowledgements section.**