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Title: Infants, children, youth and young adults with a serious illness in British Columbia: a population- based analysis using linked administrative data

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Reviewer 1: Dr. Lorna Fraser, University of York, York, UK

The authors present a very useful population-based analyses of children with serious illness in British Columbia. I have made some suggestions below to improve the clarity of the paper.

Major comments:

1. how did you mange children with multiple diagnostic categories?

   We decided to choose the modal diagnosis because it drove most of the encounters. There were very few cases where we had more than one modal diagnosis for an individual in a year, and in those cases, we assigned those people to the taxonomic unit "Otherwise Specified".

2. Justification for combing stable and unstable-ED as one group for the modelling - suggest a sensitivity analyses with stable as the reference group to assess robustness of this

   Thanks for your comment. We agree that explaining our rationale is necessary. We have included an explanation of why we combined stable and unstable-ED on the first paragraph of the modelling sub-section within methods. At least 40% of the population in the study used an emergency department within each year (Table 2). This may have been for relatively minor conditions or urgent needs unrelated to underlying serious illness. For this reason, we found that grouping unstable-ED with more serious presentations substantially and misleadingly increases the number of ICYA identified as unstable.

3. I would also question the use of 20–25-year age group as a reference - there is growing body of literature showing the increase in healthcare use after transition to adult services - again I would suggest a different childhood reference group as a sensitivity analysis to assess robustness see http://dx.doi.org/10.1038/s41390-022-01975-3

   Thank you for your comment; it was helpful to reconsider the choice of reference category for age. We have changed the reference group to the second youngest category which aligned with previous related research.[1]

4. It would be good to pull more international literature into the discussion

   Thank you for your comment. Along with another related comment, it helped us reflect and we agree that including more international literature enriches the discussion, and thus, we have added this paragraph to the interpretation section:

   "*Our work aligns with recent findings outside of North America. Korean researchers identified similar results to ours with a prevalence of 95.5/10,000 children with life-limiting conditions.*[32] *Their data included the stable, non-hospitalized group so the prevalence is expected to be larger. They also found that infants make up the largest group by far. In an examination of PICU data in the UK, children with serious illnesses*

comprised the majority of admissions (58%) and of deaths (73%).[33] For discharged survivors there was a higher 1-year mortality compared to patients without these diagnoses. These findings highlight the mortality risk for children with serious illness and why engagement with palliative care would be beneficial."

5. comment on the discussion about the additional data items that would be helpful for future studies
   e.g to measure complexity e.g., https://openresearch.nihr.ac.uk/articles/2-27

   Thank you for your comment. We have expanded the interpretation section as follows:
   "Additionally, future research should include indicators of the burden on the health care system and medical complexity to inform allocation and service planning."

Minor comments:

1. when grouping continuous variables into categories using quintiles - the quintile is the cut off not the category itself - you are creating five equal categories using quintile see Bland et al BMJ 1994 https://www.bmj.com/content/309/6960/996.short

   Thank you for this observation. We have corrected the text (demographics sub-section within results) and tables 1 and 4.

2. For a non-Canadian reader it would be helpful to have more information about the datasets used on this study.

   We have included an explanatory table as appendix 1.

Reviewer 2: Dr. Katherine Nelson, The Hospital for Sick Children

Overall: Ms. Castro Noriega and team should be commended for taking on such a challenging task: assessing the prevalence of children, youth and young adults with serious illness in British Columbia, because not only did they attempt to describe the number of individuals with serious illness diagnoses, but also to quantify clinical instability. Specialized pediatric palliative care services are ideally targeted to support children during times of stress, which often correspond to increased clinical instability. While any ICYA with a serious illness would theoretically benefit from palliative care support, understanding how many of those children are clinically unstable during a given year is likely a more reasonable target for pediatric palliative care capacity (as presumably child who are stable will not require much support).

As described below I was a bit unclear on some of the methods; further description of the modeling strategy (which would be fine to put into an appendix if space constraints) would be very helpful.

We have edited the first paragraph of the modelling sub-section within methods to clarify the modelling strategy. It now reads as follows:

"We created a binary outcome variable collapsing Stable and Unstable-ED in one group, and Unstable- Hosp, Deteriorating and Died in another. Unstable-ED was considered similar enough to Stable to be grouped together because in BC there are many reasons people go to the ED aside from the severity of the illness (e.g. out-of-office hours presentation, long waiting times to see a clinician). We used multilevel logistic regression models with random intercepts to model risk of instability, accounting for clustering of data within individuals and possible dependence across years. Sex, age group, socioeconomic status and taxonomic unit were included as predictors. We report

univariable and multivariable models."

However, the model was not the most important aspect of this study's findings to me—the quantification of this gap between what is often identified as the goal (all ICHYA with serious illness) and a more realistic goal (ICHYA with clinically unstable serious illness) is a critical number for health systems planning and could be emphasized more specifically in the abstract and manuscript.

Currently, service planners are looking broadly at all ICYA with serious illnesses, at least in British Columbia. We agree that the critical number right now is for the most unstable, but in the future we hope to be able to serve more.

In addition, a bit more comparison between this study's findings and other published literature would help contextualize these results.

Thank you for your comment. We have expanded the interpretation section to include comparison with other studies. The interpretation section now has an addition that reads as follows:

"*Our work aligns with recent findings outside of North America. Korean researchers identified similar results to ours with a prevalence of 95.5/10,000 children with life-limiting conditions.[32] Their data included the stable, non-hospitalized group so the prevalence is expected to be larger. They also found that infants make up the largest group by far. In an examination of PICU data in the UK, children with serious illnesses comprised the majority of admissions (58%) and of deaths (73%).[33] For discharged survivors there was a higher 1-year mortality compared to patients without these diagnoses. These findings highlight the mortality risk for children with serious illness and why engagement with palliative care would be beneficial."*

Major comments:
-My interpretation of what your modeling strategy (which may be wrong) is that you redefined the categories in the Jarvis study, then assigned each child one value based on the highest level of healthcare utilization recorded in the DAD during a given fiscal year. Then you collapsed the 5 categories into a binary variable, essentially sick (hospitalized/ICU/died) vs. not sick (emerg only/stable) so that each person in the cohort being assigned up to 5 outcome variables (1 per year in your study). Then you built a multi-level model with a random intercept to allow individual-level variability.

This is correct.

A couple of questions:

1. How did your account for repeated measures (i.e., an individual child having multiple outcome variables)? In the Jarvis study, they used a multi-level modeling strategy that clustered by individuals. When you describe this study as a repeated cross-sectional analysis and didn't mention clustering, I wondered if that meant you treated each year as independent. If your study did differ from the Jarvis study with respect to this question of clustering, adding a reference to the methods section justifying this approach (treating fiscal years as independent samples) would be helpful to us non-statisticians trying to understand your complex methods.

   We used a multilevel modelling strategy that clustered by individuals. We have edited the first paragraph of the modelling sub-section within methods for clarity. We realize the description of the study as repeated cross-sectional was confusing and have edited text describing study design accordingly.

2. Did you perform any sensitivity analyses to assess the impact of your assumptions? (e.g., testing the implications of giving each child a single outcome variable per fiscal year, and testing the
implications of collapsing the 5 categories into a binary variable). If yes, please describe them. If not, please describe in the limitations how these assumptions could have influenced your findings.

We appreciate your comment and agree that these are limitations of our study. We have added text to the first paragraph of the limitations sub-section within interpretation to address this comment:

"By assigning each ICYA a single outcome variable per fiscal year we have missed more granular details on periods of stability/instability that these patients experience. The annual information presented is useful for service planning, but other approaches are needed to model individual disease trajectories. Collapsing clinical stages into a binary variable was necessary due to small numbers, but obscured more subtle differences in severity levels."

3. It sounds like you did complete case analysis (i.e., you excluded patients from the model if they had any missing data). When you describe in results that <1.8% per year were missing socioeconomic data, I was unclear if your complete case analysis meant that you excluded a child completely if they were missing data for any year or if you included them for the years that they had complete data. If the former, then please report the total number of children excluded from the cohort for missing data. If the latter, then I wonder if it would make more sense to include a "missing" category in your model for SES instead of eliminating their data for just a single year. (That said, please don't re-run the models solely to add a "missing" SES category—given your sample size, it's unlikely to have a substantial effect on the findings.)

Thank you for this observation. We re-ran the model to include a change in a reference category, and used the opportunity to add a ''missing'' category for SES. While it is true the results do not change markedly, we think this is important to include because missing SES data is not likely to occur at random.

As this study was modeled on the Jarvis study, it would be helpful to understand how your findings were aligned and where they varied from that study's findings. Did they find similar rates of patients who were clinically unstable and might benefit from palliative care. (Additionally—just an idea, feel free to ignore--a graphic representing the main finding of the study (the number of ICYA vs. the number of ICYA with clinical instability vs. the number currently who currently receive palliative care services in BC) would help guide the reader to see the bottom line amidst the many tables of data). Is there data from jurisdictions other than Scotland that could help generalize these numbers further?

Thank you. We have substantially edited the interpretation section to explain how findings align with Jarvis and other international literature, as described above. As we already report four tables and now have four appendices we have not added an additional figure. However, we believe edits to the interpretation section help represent these points more clearly to readers.

Minor comments:

- Abstract, Results: Would it be clearer as— "~60% presented [with] perinatal…"?

We have changed that sentence to:

"Approximately 2,500 ICYA were hospitalized with a serious illnesses diagnosis each study year, of which ~50% were infants, ~60% with perinatal or congenital diagnoses."

- Introduction, p3 line 10: When you reference "complex care," are you intentionally invoking the clinical specialty? Or do you mean "coordinated care" or "complex ongoing care." (Basically, would be helpful to rephrase unless you intend to convey that PPC provides complex care, as a complex care team would.)

  We have changed the term "complex care" to "comprehensive care" in the first paragraph of the introduction.

- p3, line 47: 1"in-hospital consultation" isn't a place as the other items in the series are. Please consider changing to "in hospital."

  We have changed the phrasing of the setting sub-section within methods to:

  "BC and Yukon are served by Canuck Place Children's Hospice, a province-wide PPC program. Canuck Place provides respite, specialist symptom management, end-of-life care and bereavement in two hospice locations, in families' homes[17] and also through BC Children's Hospital inpatient and outpatient services[18] and regional hospitals.[19]"

- p4, line 5: What does "MSP" stand for?

  We have spelled out the full term (Medical Services Plan) in the data sources sub-section within methods.

- p4, line 17: By "with a serious illness diagnosis… during an inpatient hospital visit" do you mean a new diagnosis (e.g., first visit with diabetes) or 1+ diagnosis codes for a serious illness on a hospitalization record?

  Thanks for your question; it is helpful for clarity. We included hospitalizations with any diagnostic codes, not only new diagnoses. We have reworded this sentence in the study population sub- section of the methods. We also included a reference to appendix 2 with more details on diagnostic codes for readers looking for additional information.

- p12, line 6: It sounds like you imputed diagnoses when there was no hospitalization during a given year. I'm assuming the backwards imputation (i.e. if a patient had a diagnosis in 2017, you assumed they also had it in 2016) was not universally applied to account for new-onset diagnoses, but the rules around this were not clear from the sentence describing it: "For the model, if a person did not have a primary diagnostic category in a given year, we assigned the taxonomic unit from the closest preceding year if applicable, or the closest subsequent year otherwise." Would you consider adding a figure or a more fulsome description to the Appendix explaining how this worked in more detail?

  Thank you for this suggestion. We included a figure (Appendix 3) explaining how we assigned taxonomic unit when there was no diagnostic category in a given year.

- p6, line 35: Can you given examples of the adult-onset conditions that you identified? (If this is intended as an explanation of the pattern rather than a description of the data, may be better suited for the Discussion section.)

  We have edited this text to include examples of conditions, and moved it to the interpretation section for clarity. The paragraph now reads as follows:

"We noted that after infancy there is a decline in hospital-linked cases until adolescence and early adulthood. We hypothesize that this is due to new onset conditions more common in older individuals (e.g., Hodgkin's Lymphoma) and deterioration from childhood conditions that led to a hospitalization (e.g., palliated congenital heart disease)."

- p8, line 34: It's hard for me to know what to interpret from your comment that you were unable to duplicate the Jarvis approach specifically—can you briefly elaborate on the point? What about your approach was different and why? (Or else it would be reasonable to strike the comment and instead explain how the methodologic choices you made would potentially influence the results.)

  We appreciate your suggestion and have deleted the last paragraph of the limitations section. We explain how the methodologic choices we made would potentially influence the results throughout the paper, for example, under the variables sub-section within methods:

  "Initially, we captured a large group of neonates using the described methodology, more than we report here. Additional exploration found that many were assigned ICD-10 code P28.5, Respiratory failure of newborn; however, in most cases where this was the only code assigned, or when it was combined with six other specific ICD-10 codes (Appendix 4), there were no further Emergency Department (ED) visits or urgent hospitalizations, suggesting that their health improved. We removed these patients from the study as they would not need PPC."

References

1. Jarvis S, Parslow RC, Carragher P, Beresford B, Fraser LK. How many children and young people with life-limiting conditions are clinically unstable? A national data linkage study. Arch Dis Child. 2017 Feb 1;102(2):131–8.