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Title	Outcomes after emergency department use in patients with cancer receiving chemotherapy in Ontario, Canada: a population-based cohort study
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Reviewer 1	Balthasar Hug
Institution	Internal Medicine, Luzerner Kantonsspital, Lucerne, Switzerland
General comments (author response in bold)	Grewal et al have written a concise and clinically important paper about ED visits by patients with cancer under ongoing chemotherapy. They conducted a population-based retrospective study with administrative data from 218,459 ED visits made by 87,555 patients between 2013 and 2017. The study is well done and well understandable. There are some points that need clarification as outlined below. **We thank the reviewer for these comments.** 1. Inclusion age: in the abstract it's "patients >17 years" and on p.3, line 33 it's "Adult patients aged 18 years and older". Thank you for clarifying and updating this information so it's consistent. Where was the cutoff age, after the 18th birthday or after the 17th birthday? **Thank you for pointing this out – we apologize for the oversight. We included patients aged 18 years and older in the study. We have changed the abstract so that it is consistent with the methods section.** 2. ICES: this institute appears only as abbreviation in the text. Thank you for writing this out as "Institute for Clinical Evaluative Sciences" once and explaining in at least a sentence to the international reader what type of institute this is and referencing its online appearance. **In 2018, the institute formerly known as the Institute for Clinical Evaluative Sciences formally adopted the initialism ICES as its official name. This change acknowledges the growth and evolution of the organization's research since its inception in 1992, while retaining the familiarity of the former acronym within the scientific community and beyond. Therefore, we have not written out ICES. On page 3, we have updated the methods to explain what type of institute ICES is.** 3. Databases: the four databases OCR, NACRS, DAD and OHIP are described in the appendix. In my view the authors should write a few sentences about the four databases and above all their linkage procedure in the manuscript text on p. 3 in the paragraph "data sources". The sentence that the databases were linked using encoded identifiers and analyzed at ICES is not enough in my view. These procedures are important to understand for international readers, even if Ontario is in the lucky situation to have all these databases at its disposal and having them already linked. **We thank the reviewer for this comment. As discussed above, we have moved information regarding the main databases used in this study and their descriptions from the Appendix and into the methods section on page 3 and 4.** 4. Exclusion of certain study participants: on p. 3, two bottom lines we read "We excluded visits in an Ontario ED that was not open 24 hours per day or visits to an urgent care centre (n=5,538),…" Why were these patients excluded? These

two exclusion reasons need a short explanation since they are not self-explanatory.
As we described above, we excluded visits to urgent care centres and EDs that are not open 24 hours per day because these are typically urgent care centres that see a much lower acuity patient population than a true ED. We have added this justification to the methods: "We excluded visits in an Ontario ED that was not open 24 hours per day or visits to an urgent care centre (as these are typically urgent care centres that see a much lower acuity patient population than a true ED".

5. Income: On p.5, second line we learn that the income quintile was used as covariate for the regression model. Thank your for a short sentence where that information derives from.
Income quintile was determined by the neighbourhood income quintile based on the patient's postal code at the time of the ED visit. This has been clarified in the supplementary appendix as follows: "Neighbourhood income quintile was determined by patient postal code".

6. On p. 8, second paragraph the authors expand on the very important point of how to prevent readmissions in these patients. Since the 1990's there is an ongoing discussion about risk stratification and oral antibiotic treatment in neutropenic cancer patients. Interestingly, the authors just reference #18 and 19 although there is vast information available and this is low hanging fruit for these authors to discuss. Authors like Kern et al. provide a lot of information about this topic and the authors should expand more on how to treat these patients in ambulatory settings (Kern, Cometta et al. 1999, Kern, Marchetti et al. 2013).
Thank you for this suggestion. We have incorporated this feedback into the implications section of the manuscript on page 10. We discuss that previous work has shown that some low-risk febrile neutropenic patients can be safely treated with oral antibiotics and that future work should focus on whether this can occur in an ambulatory setting. Specifically, we have edited the paragraph to read: "Previous studies have shown that some low-risk febrile neutropenic patients can be safely managed with oral antibiotics.20,21 Future work should focus on determining which patients with infection or fever can safely avoid an ED visit (e.g., patients with non-systemic infections such as a cellulitis or otitis media) and the best non-ED setting to be safely worked-up and treated." We have also added in the references the reviewer has suggested.

7. On p. 9, first paragraph, the authors make an important point about pain control or lack of it which leads to more hospital admissions. Here it would be very interesting to know if there are any guidelines in these hospitals and practices in Ontario? Furthermore, this could be a future research topic (How good is pain control in cancer patients?).
To our knowledge, there are currently no province-wide guidelines for treating cancer-associated pain in the emergency department. We agree, this would be an excellent future research topic. We have added a sentence to the page 11 in the section on pain control: "Furthermore, future research and guidelines for treating cancer-related pain in the ED may be useful".

8. Limitations section, p. 9-10: A point should be added here that generalizability may be hampered to other health care settings outside of Ontario

	due to different treatment patterns such as the mentioned ones in the discussion about the US with much higher readmission rates. **We have added a limitation regarding generalizability of this study outside of Ontario: "This study examined ED use by patients within Ontario, therefore, the findings may not be generalizable outside of Ontario."** 9. The second sentence is a repetition of results that do not belong in the conclusions or say "..approximately a third of ED visits…" **We have edited the second sentence of the conclusion on page 12 to say "approximately one third of ED visits resulted in hospital admission".** 10. I would be more specific in second half of the last sentence: "The results of this study highlight opportunities for future research, including the identification of high-yield groups and diagnoses to target for future care interventions." It's about fever and pain as described by these authors and some GI side effects. Suggestion: ".. including the identification of targets for future care interventions mainly the control of pain and GI symptoms as well as ambulatory antibiotic treatment in febrile patients." or the like. **We thank the reviewer for their comments. We have updated the conclusion on page 12 to be more specific of which high-yield groups/diagnoses should be targeted for future studies. We have changed the last sentence of the paragraph to read: "The results of this study highlight opportunities for future research, including the identification of targets for future care interventions around infectious, gastrointestinal and pain diagnoses".** 11. Outcome variables: in the last three lines on p. 4, the numbers of the secondary outcomes are not correct going from 1) to 2) to 4) to 6). Thank you for your correction. **Thank you for this correction. We have corrected the numbering of the secondary outcomes from 1 to 3.**
Reviewer 2	Karen Urbanoski
Institution	Social and Epidemiological Research, Centre for Addiction and Mental Health, Toronto, Ont.
General comments (author response in bold)	1. A clear statement of rationale is missing. The background section describes what prior studies have found, but does not identify a gap in the literature. The authors cite evidence to demonstrate that cancer patients are more frequently seen in the ED than other patients, and that fever, GI complaints, and pain are common reasons why. What is not known on this topic that this descriptive study will add? **Many of the previous studies that have examined emergency department use by cancer patients have reported on a small cohort of patients or have been conducted using insurance databases in the United States that may not capture the entire population of interest. Using ICES data we have the unique opportunity to report on emergency department use by cancer patients in Ontario, which is Canada's most populous province. Furthermore, because of the universal nature of our health care system, we can report on emergency department use and outcomes at a population-level. We have updated the final paragraph of the introduction on page 2 to improve the rationale of our study: "Previous studies have shown that fever, gastrointestinal complaints and pain are common reasons patients with cancer are seen in the ED and/or admitted to hospital.9-11 However, few**

	studies have been conducted at a population level, or report on Canadian data". 2. The second paragraph in the Introduction summarizes levels of ED use among cancer patients, but these aren't contextualized with rates in the general population or other patient groups. If these figures are meant to establish that rates of ED use are elevated in cancer patients, then it would be helpful to state this explicitly. **We have added a sentence at the beginning of the introduction to state that "emergency department use is higher among cancer patients compared to the general population".** 3. It would be helpful to provide the reason why ED visits with a primary dx of radiation or chemotherapy are excluded in the Methods section (top of p.4). It is stated in the limitations section, but it would be helpful earlier on. **Thank you for this comment. As described above, we have added the justification for excluding ED visits with a main diagnosis of radiation or chemotherapy earlier to our methods: "We also excluded ED visits where the main diagnosis for the ED visit was listed as radiation or chemotherapy to ensure scheduled visits for chemotherapy or radiation were not included in the analysis".** 4. The rationale for the median LOS in the ED as a secondary outcome is unclear. It seems conceptually different from the other outcomes examined in the study. Is it a measure of acuity, reflective of ED efficiency/wait times, or something else? Also notable is that it isn't taken up/interpreted in the Discussion. **We agree with the reviewer, and as such we have decided to remove ED length of stay as a secondary outcome. Therefore, we have removed the mention of it as an outcome from the abstract and methods section of the manuscript. In the results section, we have left in the median ED length of stay for patients, as this may be of interest to some readers.** 5. Please clarify if income quintile is individual or neighbourhood level. **Income quintile was the neighbourhood income quintile based on postal code. This has been clarified in the manuscript as follows: "demographics (age, sex, neighbourhood income quintile)".** 6. There is missing punctuation on p. 7, line 21/22. **Thank you for this correction. We have added in a period between the two sentences in question on page 8.** 7. Following from the first comment above, the text in the Discussion section notes that findings are all consistent with prior evidence. What is the added contribution of this study? Do any of the findings build on what has been shown previously, provide replication in a larger or different sample, etc.? **This study adds to the literature by providing Canadian, population-level data to replicate findings from previous smaller studies. As discussed previously, we have edited the introduction to provide a stronger rationale of our study: "Previous studies have shown that fever, gastrointestinal complaints and pain are common reasons patients with cancer are seen in the ED and/or admitted to hospital.9-11 However, few studies have been conducted at a population level, or report on Canadian data". Furthermore,**

	we have updated the conclusion to state "In this Canadian, population-based study, we found that one in four ED visits were due to infection/fever and approximately one third of ED visits resulted in hospital admission".