Reviewer’s report

Title: The healthcare costs of intoxicated patients who survive ICU admission are higher than non-intoxicated ICU patients: A retrospective study combining healthcare insurance data and data from a Dutch national quality registry

Version: 0 Date: 28 Jul 2018

Reviewer: Shannon M. Fernando

Reviewer's report:

Thank you for allowing me the opportunity to review this paper.

I want to congratulate the authors on performing a very interesting study, with interesting results. These authors sought to characterize the costs of intoxicated patients admitted to the ICU in the year prior, and the year following ICU admission. This is a population of patients that are commonly seen in the Emergency Department and are often admitted to the ICU. Unlike previous studies in this population, the authors used a large sample of patients from a national database, and compared these patients to a matched cohort of non-intoxicated ICU patients. They found that the patients contribute appreciable costs, and that costs are correlated with pre-ICU morbidity. Though the results are interesting, and the study is well done overall. However, there are some important areas for improvement, which may help increase the strength of this study.

Major Comments

Page 6, Line 5 - It's interesting that the authors chose not to match on the basis of illness severity (APACHE), especially since that data seems to have been available in the database. Cost is obviously heavily influenced by severity of illness and death (see Kramer, Crit Care Med, 2017 for a recent example). There are pros and cons to not matching on the basis of severity of illness. The obvious con is that an important confounder of total cost has not been included. Therefore, we do not know whether the differences in cost may simply be attributable to illness severity (for example, an acetaminophen overdose with multi-organ failure requiring transplant is likely to have a significantly different post-ICU course than a patient who simply took an overdose of sedatives and required a brief amount of mechanical ventilation for airway protection). I think the authors should comment on this, and justify their reasons for now including APACHE, especially since Table 1 makes it clear that there are significant differences in illness severity.

I'm very much appreciative of the flow diagram (Fig 1). I believe these should be a necessity in any large database/cohort study. Could the authors please indicate in the diagram how many patients were excluded, and for what reason(s) (e.g. because of missing data or death)? This will help contextualize the proportion of patients that were utilized in the analysis.
It is not clear to me from the Methods how the "1 year post-ICU" course was determined. It seems like patient costs during 2013 (year of ICU admission) were compared to patient costs in 2014. But a patient admitted to ICU in January 2013 is going to have different costs in 2014 than a patient admitted to ICU in December. It appears that the costs are counted on an individual patient basis for the following calendar year, but this needs to be made more clear in the Methods.

Table 1 - I'm very confused with some of the terminology in Table 1 for the xenobiotics. What do you mean by "street drug"? Any drug can be a street drug. Also, the categories are rather broad. Antidepressants could include things like TCAs or Wellbutrin (which are frequently lethal), or SSRIs, or SNRIs, etc. It's understandable that greater granularity is not available, but the authors should include this as a limitation. Finally, presumably by "poisoning", you mean deliberate poisoning by another party? If so, I would be more clear. Often in the literature, "poisoning" is used interchangeably with "intoxication".

Page 10, Line 42 - What did the intoxication patients die of in 2014? I think this would be very interesting information.

Some Discussion points should be touched on further:

The most recent studies on this topic by Sut et al (Clin Tox, 2008) and Fernando et al (J Intensive Care Med, 2018) found that these patients are actually cheaper than compared controls, during their ICU stay. Your study provides important long-term data. Why do you feel that these patients are cheaper during their ICU stay, but more expensive in the long-term?

Second, why do you think the sedative overdose patients had more expensive costs in the year following?

Minor Comments

Page 3, Line 56 - Would change to: "In the Netherlands, intoxicated patients make up…"

Page 5, Line 14 - What were the study periods of the entire database? What was the reasoning for choosing 2013 for the comparison?

Page 8, Line 1 - I appreciate the use of a GLM for cost effect determination. Would the authors be able to provide more data on the GLM? (i.e. log-link, gamma dist, etc.).

Table 1 - Is duration of mechanical ventilation available? If so, please provide as this would help contextualize the costs.
Thank you again for the opportunity to review this paper, and congratulations again to the authors.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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