Dear Dr. Fernando,

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We are interested in proceeding with it provided you are willing and able to revise your paper as explained below in the report from the manuscript meeting. In revising the paper, please pay special attention to the report from Professor Kurth. He will need to be satisfied with the revision in order for us to move forward with acceptance. If the recommendations of other reviewers differ from those of Professor Kurth, please be guided by Professor Kurth’s suggestions.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Thank you for entrusting us with your work. This is a very interesting research question and we are interested in the outcome whether it is positive or negative.

Sincerely,

Dr Elizabeth Loder

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**Report from The BMJ’s manuscript committee meeting**

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Present: John Fletcher (chair); Richard Riley (statistician); Tiago Villanueva; Joseph Ross; Wim Weber; Jin-ling Tang; Jessica Kimpton; David Ludwig; Nazrul Islam; Elizabeth Loder

Decision: Request revisions before final decision

* We were very interested in the research question and could not find much in the literature about this. It is timely in the context of the pandemic.
We wonder if you should take more account of time spent in ICU. It is one thing to spend 2 or 3 days in ICU following an operation and another to spend 2 months due to covid-19 or some other protracted illness.

The absolute risk difference is quite small (0.2% vs. 0.1% for suicide, 1.3% vs. 0.8% for self-harm). You include a large number of patients (ICU survivors n=423,060 and non-ICU survivors n=3.08million) with minimal missing data.

Given the small effect size, we worry about confounding. Looking just at the key data in the Abstract, the raw data for ICU data show about 2-fold higher incidence of the adverse events. However, the adjusted HR seem surprising small, hovering about 1.2. We would like your interpretation to be more cautious in light of the potential for residual confounding. Might a "tipping point analysis" be helpful to see what level of association with the confounders would make the reported association "non-significant"?

Isn't it vital to know the reason for the admission in the first place? Some people in ICU might be there because of attempted suicide and it would be no surprise that these people are at risk of subsequent self harm. Are you able to provide any information about reasons for admission? Even if only for a subset of admissions this might address concerns of the reviewers.

There is confusion between the causal and predictive components of the models. You alternate language in this regard. These two need to be clearly differentiated. Also, there is issue of Table 2 fallacy in terms of interpretation of the effect estimates from the risk factor model. The propensity score approach suggests that causality is more of interest for the main variable of ICU, but we wonder if causal diagrams would be helpful if so.

Were non proportional hazards considered? We think this is critical, as the HR is unlikely to be constant over time.

We were pleased that you accounted for competing risk of non suicide death when deriving the absolute risk and rates, though it is not always clear. E.g. in abstract “During the study period, the crude incidence (per 100,000 person-years) of suicide, self-harm and their composite among ICU survivors were 41.4, 327.9, and 361.0, respectively, compared with 16.8, 177.3, and 191.6” – did these account for competing risk of death from not a suicide?

How were missing data handled in the analyses? We think missing data are < 1% but this needs clarifying

Figure 1 – need to clarify in the legend if these were derived accounting for competing risks and whether they relate to the post-propensity score analysis.

The objective says you examined the association between ICU admission and suicidal risk, which is very different from the association between surviving critical illnesses and suicidal risk (as in the title and the conclusion). It conveys a very different messages if the conclusion is that ICU admission (as opposed to surviving a critical illnesses) is associated with a higher suicidal risk.

We are interested in seeing other sensitivity analysis using alternative methods of PS (such as IPTW, especially stabilised version of the IPTW) to see if these estimates hold. It will be equally important and interesting if they don't.

Our patient editor notes that "The patient reviewer suggests including advocates in dissemination and this is excellent advice."

Please also include a statement about patient and public involvement in determining the research question, or, if this was not possible, briefly describe the barriers to implementing this. This can be placed in the methods section of the paper.
In your response, please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
The present manuscript "Suicide and Self-Harm In Adult Survivors of Critical Illness- A Population-based Cohort Study" is an important addition to the critical care medicine literature. It presents new, previously unreported (I could not find any previous publications) and meaningful findings- that ICU survivors especially with pre-existing psychiatric illness, lower socioeconomic status, ICU life support interventions and hospital discharge to home have a higher risk for suicide and self-harm. Although the prevalence of this problem is not high, the discovery has major health care implications for disease prevention. The authors might want to add the hypothesis of their study.

Specific comments:
Page 12, lines 12-25- Did "ICU survivors" include all patients that were hospitalized in the ICU and survived to hospital discharge from January 1, 2009 until December 31, 2017?
Page 13, lines 3-9- Patients with shock and/or requiring vasopressor or inotropic treatment should also be included. These patients certainly have longer ICU durations of stay and reference 11 (Sivanathan) notes "Patients exposed to mechanical ventilation or longer ICU stays may be at higher risk of subsequent mental illnesses.” In addition, factors associated with depression in ICU discharged patients included cumulative doses of dobutamine (Calsavara AJ, et al. Braz J Psychiatry 2020; S1516-44462020005032203. doi: 10.1590/1516-4446-2020-0986). Patients with shock and/or requiring vasopressor or inotropic treatment seem more prone to develop mental issues than patients undergoing renal replacement therapy.
Page 13, lines 14-36- Although the terms "completed suicide" and "self-harm" are defined by previously validated ICD-10 codes in Supplemental Table 2, it might be helpful for the reader to better understand what is involved by providing a few examples in the text as to what ‘self-harm’ includes. As I read the manuscript it wasn’t that clear including whether suicide attempts were included in self-harm.
Page 14, lines 8-50- It is not clear who the 3,081,111 "non-ICU hospital survivors" represent? Do the 3,081,111 "non-ICU hospital survivors" include all patients that were hospitalized who never required ICU and survived to hospital discharge from January 1, 2009 until December 31, 2017 or rather those patients that were hospitalized who never required ICU and survived to hospital discharge from January 1, 2009 until December 31, 2017 chosen for the overlap propensity score weighting? If the latter, how many total "non-ICU hospital survivors" were hospitalized who never required ICU and survived to hospital discharge from January 1, 2009 until December 31, 2017?
Page 15, lines 23-25- "receipt of invasive therapies (invasive mechanical ventilation or renal replacement therapy)".... I think "undergoing invasive therapies..." is more appropriate. This appears in many other sections of the manuscript which should also be changed.
Page 15, lines 42-44- It is not clear what Supplemental Table 3 adds.
Page 17, lines 26-29- Why change the heading order for table 3? Unless there is a good reason it is best to be consistent with the same heading order for "suicide, self-harm, or the composite of both" in all the tables.
Page 18, lines - Please explain the significance of the heat map and what it means. Perhaps an example in the figure would be helpful as most readers will not clearly understand what it means.
Page 18, lines 53-55 to Page 19, lines1-50 – "Strengths and Limitations of Study”- better to put at the end of discussion. I believe the authors should emphasize in the strengths the fact that their findings represent new information.
Page 20, lines 12-18- "our work shows that ICU survivors who go on to complete suicide and self-harm are markedly different from the patients with chronic physical morbidity following discharge.” These ICU
survivors also seem to be less severely ill as they had more patients with lower Charlson Comorbidity Index scores and less patients with higher scores.

- Originality - New, previously unreported (I could not find any previous publications) and meaningful findings- that ICU survivors especially with pre-existing psychiatric illness, lower socioeconomic status, ICU life support interventions and hospital discharge to home have a higher risk for suicide and self-harm.
- Importance of work to general readers - This work should matter to clinicians, patients, teachers, and policymakers. A general journal is the right place for it as general physicians who treat these patients will not know of this work if it is published in a specialty journal.
- Scientific reliability- Reliable.
- Research Question – Should be more clearly defined as it is appropriately answered.
- Overall design of study – Excellent.
- Participants studied - Adequately described.
- Methods - Adequately described.
- Results - Answers the research question, credible and well presented.
- Interpretation and conclusions - Warranted by and sufficiently derived from the data. Message is clear.
- References - Up to date and relevant. No glaring omissions.
- Abstract/summary/key messages/What this paper adds - Reflect accurately what the paper says.

Charles Sprung MD

Additional Questions:

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Please enter your name: Charles Sprung

Job Title: Director Emeritus, GICU

Institution: Hadassah Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No
A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Comments:
I found the topic of great importance. Every person who undergoes an ICU procedure - as well as their carers and doctors - should be aware of it, especially if they are in the groups at major risk. The understanding of the relation between ICU, self-harm and suicide could help improve the support provided to ICU survivors. The aims of the study are well described. Although a lay person could find the methodological part challenging, I think that the paper’s key elements are sufficiently explained.

Looking at the Supplemental Table 3, it seems there is a decrease in the numbers of self-harm and suicides during the years of the study. This could be an important finding that is not taken in consideration by the Authors. An investigation on the causes that lead to this decrease, could help the understanding of the factors associated with higher and lower risk of self-harm and suicide.

In the subsection Patient, in Methods, the sentence “For patients with multiple hospitalisations, we only considered the first admission during this time period” is not completely clear. I don’t understand if for “this time period” the Authors are referring to the entire time period of the study or the period in which one patient was subject to multiple and consecutive hospitalisations. In any case, I suggest identifying as ICU survivors the patients underwent to multiple hospitalisations in which the ICU admission is not necessarily the first one.
In relation of future research, I suggest that the Authors could investigate the impact that the availability of palliative and end of life care for ICU survivor could have in the relation between ICU hospitalisation and self-harm and suicide. Furthermore, I suggest introducing a stratification of ICU survivors based on a measure of quality of life before and after the hospitalisation.

With reference to patient/carer involvement, the Authors state that they will seek to engage several key local policymakers and national stakeholders. I invite the Authors to engage with patients and cares organization involved in the field as well. This could be useful for having a broader divulgation of the study results and to establish a direct contact with patients and carers that could lead to a direct involvement of them in future works.

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Please enter your name: Franco Cappai

Job Title: Biomedical Research Support Unit - Project Manager

Institution: Sardegna Ricerche

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Would you like to be accredited by ORCID for this review?: No

Reviewer: 3
Comments:
This review was conducted by Christine Ulbricht and Julie Hugunin.

This is a potentially important study on risk of death by suicide and self-harm following discharge from the intensive care unit. Although this study has potentially important implications, especially when considered within the Zero Suicide framework, concerns about misspecification of the propensity score model diminish enthusiasm about this work. This manuscript may require additional statistical review. Additional concerns include the need for clarification on the definition of certain covariates and outcomes, as well as a few typos and formatting suggestions.

Specific comments and questions designed to improve the overall quality of this work are as follows.
2. Minor typo: “We identified adult patients admitted to an ICU setting ("ICU survivors") using previously validated algorithms from the Canadian Institute for Health Information Discharge Abstract Database, and compared these patients to those admitted to a hospital setting who never required ICU ("non-ICU hospital survivors").”
3. A brief explanation as to how or why you chose the life support interventions received during hospitalization would be helpful.
4. Please briefly describe the interpretation of the Charlson Comorbidity Index (CCI). In the results section prevalence of the CCI are given, but the reader may be unaware of the meaning of 3-4 or greater than or equal to 5.
5. Clarification is needed regarding how the overlap propensity score weighting was conducted. How were the propensity scores constructed? As the probability of receiving ICU care (i.e., the exposure/treatment) or as the probability of suicide and/or self-harm (i.e., the outcome)? What was the literature that informed which the relevant variables were used in constructing the weights (page 14,
Given the list of variables that were used to construct the weights, e.g., previous history of self-harm, it appears that the propensity scores were erroneously constructed as the probability of the outcome. For more information, see: 1) Li F, Thomas LE, Li F. Addressing Extreme Propensity Scores via the Overlap Weights. Am J Epidemiol. 2019 Jan 1;188(1):250-257. doi: 10.1093/aje/kwy201. Erratum in: Am J Epidemiol. 2021 Jan 4;190(1):189-190. PMID: 30189042; and, as cited in the manuscript, 2) Thomas LE, Li F, Pencina MJ. Overlap Weighting: A Propensity Score Method That Mimics Attributes of a Randomized Clinical Trial. JAMA. 2020 Jun 16;323(23):2417-2418. doi: 10.1001/jama.2020.7819. PMID: 32369102.

6. Were data on inpatient mental health service use available? If so, why was it not considered along with outpatient mental health service use?
7. Was any additional information about post-ICU service utilization available, particularly since those who were discharged home without homecare were more likely to die by suicide or experience self-harm?
8. How was the proportional hazards assumption evaluated for the Cox models?
9. Were there any missing data?
10. Patients discharged home had higher risk of suicide or self-harm, as compared to those discharged to a healthcare facility. The authors state that reduced function and cognitive impairment may account for the lower incidence of suicide or self-harm, are there any studies the authors can cite regarding the association between cognitive impairment/activities of daily living and suicide/self-harm risk?
11. Minor typo: “Identifying high-risk patients may allow inform targeting of prevention strategies”
12. Figure 1: I would recommend either removing the boxes with the icu_yn and icu_mh labels, or provide more descriptive labels on the image.

Additional Questions:

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Please enter your name: Christine Ulbricht
Job Title: Assistant Professor
Institution: University of Massachusetts Medical School
Reimbursement for attending a symposium?: No
A fee for speaking?: No
A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

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Reviewer: 4
Comments:
This peer review was conducted as a part of the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed by the Institute of Public Health at the Charité - Universitätsmedizin Berlin in cooperation with the BMJ.

Summary
This population-based cohort study examines incidence and risk factors for suicide and self-harm in adult survivors of intensive care unit (ICU) using data from Ontario, Canada. The incidence of suicide and self-harm is higher in ICU-survivors than in non-ICU hospital survivors. Using overlap propensity score weighted cause-specific Cox proportional hazards models they found increased relative hazards of suicide or self-harm among the ICU-survivors compared to the non-ICU hospital survivors. History of mental health diagnoses is one factor that is associated with a higher risk of suicide or self-harm.

This is a well-written paper that covers an important topic for patients admitted to an ICU. Several aspects, however, should be considered by the authors that we outline below.

Importance and originality
1. The authors aimed to estimate the effect of ICU admission on the outcomes suicide and self-harm. To estimate the association, the authors performed weighted propensity score analyses to account for possible confounding. While the primary aim of the study is of high importance for the general public, the comparison groups are challenging. Admission to ICU happens for strong health-related conditions and such conditions will always result in admission. Thus, exchangeability of the exposed and referent group may not be given. This may also explain some aspects of Figure 1. In this figure, it is apparent that the increased rate happens as soon as a patient is admitted to an ICU. Thus, we are concerned that the small increased relative rate is a result of residual confounding. However, investigating whether the ICU survivor population differs from the non-ICU survivor population is an important first step to evaluate which patients in the ICU may be at increased risk for suicide or self harm. But the interpretation of the results would benefit from a more detailed discussion about the potential non-exchangeability issue.

2. As a secondary aim, the authors had the goal to identify among patients admitted to the ICU those at higher risk of suicide and self harm. This aim seems much more relevant and may lead to potential preventative consequences, whereas the first aim is a necessary step but unlikely has preventative consequences as described above. To identify patients at higher risk for the outcomes, the authors had two approaches. First, they pre-selected potential "prognostic" factors and entered those in one Cox proportional hazard model. Second, the authors conducted stratified analyses based on age, performed interventions and prior mental health diagnoses. While we believe that the stratified analyses provides meaningful and valid results, the first approach may have its limitations. The authors report the multivariable-adjusted hazard ratios from the Cox model. However, the interpretation of these effect estimates is challenging as adjusted effect estimates have a causal interpretation. Prognostic factors should rather be identified by framework of a prediction model and not a model that conceptually addresses confounding. Showing multiple hazard ratios from one model is known as "Table 2 fallacy" (Westreich D, Greenland S. The table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am J Epidemiol. 2013 Feb 15;177(4):292–8), which may apply here. Thus, the interpretation of the relative hazard is challenging. We believe that partly labelling the prognostic factors "risk factors" adds to this confusion, as risk factors are generally referred to factors causing a condition of interest.

Title
Maybe it is worth considering that this study is from Canada.

Abstract
1. An explanation for the abbreviation ICU should be added to the abstract
2. We recommend a more careful interpretation of the prognostic factors.

Introduction
1. Good introduction, makes the importance of the research question clear. It may be beneficial, if the authors could focus a bit more on the preventable factors

Methods
1. Please explain what ICES stands for.
2. P12, l5: What do you mean with "Data contained in ICES is full and complete"? That there is no missing data issue? Please be more precise. How many data were missing, and how did you handle missing data?
3. P.12, l. 29: "and compared these patients to those admitted to a hospital setting who...". The word "to" is missing.
4. As this is a causal question, the authors should explain the framework to address confounding. Ideally, showing a directed acyclic graph.
5. Could the authors discuss the potential influence of hospital re-admissions? Can you find an association between the number of admissions and the suicide and self-harm risk?

6. P14, l3: "adjusting for competing risk of death due to other causes" – how did you adjust for competing risk (i.e., cumulative incidence function, or Fine and Gray, etc)? As in Figure 1 "Gray’s test is mentioned, we assume that you used Gray’s method. Could you add this to the methods section?

7. As recorded self harm has a sensitivity of 85% and the adjusted effect size indicates a small effect size, (differential) misclassification of self-harm may impact this finding. This potential issue should be discussed.

8. P13, l47 ff, the authors describe to have calculated test statistics. However, unless we have missed it, the authors do not show test statistics or P values in the paper except for Gray’s test in figure1. Please remove test statistics that you have not used and add Gray’s test.

9. The building of the propensity score model is unclear. What was the rationale to include variables to the PS model? What model was used? Please be more explicit about the weights.

10. As described above, we have some concerns about the method to identify “prognostic factors.” We recommend to use methodology of prediction models to identify predictors of the outcome or extend the stratified analysis.

11. We encourage to also evaluate the role of sex in the stratified analyses.

Results
1. Reporting some results from table 1 in text only for ICU patients, the authors do not mention the difference in age & sex between the two cohorts. Especially the difference in sex can be an issue, as men complete suicide more often in general. This should be mentioned.

2. We wonder if it would be enough to report percentage and corresponding CI without the total numbers in the text for a better readability.

3. Could the results reported on page 16 (per 100,000 person-years during the entire follow-up period) also be given in a table? This would make a comparison easier.

4. P16, l49, please do not use the term “odds” as you calculate rates.

Discussion
1. P18, l31: “propensity matching methods”: didn’t you use weighting methods?

2. P.18, l33-36, please do not show results in the discussion that you have not shown in the results section.

3. Please discuss why the relatively small effect estimates may still matter on the population level.

4. Arguments of how the outcomes can be prevented should not be concluded from the prognostic factors (as this would require adequate causal inference modeling). Please make no recommendation on strategies that have not been tested in the analyses.

Tables & Figures
1. Figure 1: labels could be improved for a better understanding, e.g. figure 1 A-C – replace icu_yn and 0/1 by proper names, please explain the abbreviation MH that is given in figure 1 D-F. Could the headings of the subfigures be given directly next to it to make it easier to see which is about which endpoint?
2. Figure 1 gives results for “Gray’s test” that is neither mentioned in methods nor results; please include it in the text or exclude it from the figure.

3. Figure 2: for the heat map it would be good to use other colors than green/red that colorblind people can read, e.g. blue/red and white for the middle.

4. Supplement table 4: Weighted Std-Diff are all 0.00000 (better <0.00001 or 10 exp XX because it’s not exactly 0).

Competing interests:
P.2, l. 39: "No support from any organization for the submitted work". Doesn’t this sentence contradict what is mentioned in the funding section about funds and support by the Institut du Savoir Montfort and the ICES.

Additional Questions:
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Please enter your name: Tobias Kurth for the Peerspectives program

Job Title: Epidemiologist

Institution: Charité - Universitätsmedizin Berlin

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: Yes
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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests please declare them here: This peer review was done under the Peer Review and Biomedical Editing Training Initiative (Peerspectives), which has been developed in cooperation with the BMJ. In total, 4 PhD students from the Charité - Universitätsmedizin Berlin and one experienced mentor reviewed this paper. All participants have agreed to the BMJ reviewer policies.

PhD Students:
1 Shafinaz Sobhan
2 Majed Kikhia
3 Boris Bouazza-Arostegui
4 Mareen Pigorsch

Mentor (takes responsibility for the review):
Tobias Kurth

Potential competing interests: TK received personal compensation from Eli Lilly and Company, Newsenselab, Teva, Total S.E., and the BMJ.

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