PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Causes of death in critically ill paediatric patients in Japan: a
	retrospective multicentre cohort study
AUTHORS	Ishihara, Tadashi

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting USA
	Competing interests: None
REVIEW RETURNED	07-Apr-2019

GENERAL COMMENTS	I mostly confine my remarks to statistical aspects of this paper.
	p. 3 - I assume these data about PICU are per capita, but that should be stated explicitly.
	p. 4 - there is a contradiction at the end of the first paragraph. I think "or ICUs" needs to be deleted.
	Table 1 (and the text about it) is really the only statistical part of this paper. There are a number of errors and omissions:
	For gender and extrinsic cause, the authors did not give the %ages.
	For age and length of stay, rather than mean and sd, it would be better to give median and MAD (median absolute deviation) or interquartile range. Both of these variables are clearly skew. Graphs of each, with a line for each group, would be good, as well.
	In the text, the authors list several tests, but they need to say which test was done on which variable, not just "depending on their distributions".
	For time of admission, referral origin and transportation, it looks like the authors tested each row. But it would probably be better to do a chi-square test - reducing 14 tests to 3.
	For "referral origin" I'm not sure of the utility of the analysis. "Previously healthy patients" by definition, cannot have come from a general ward or operating room. And, although I am not a pediatrician or public health professional, I'm not sure how this analysis matters.
	For transportation, what about the 37 patients in the chronic group who came from the general ward or the operating room? They seem to have vanished in the transportaion section. This needs to be made explicit.

REVIEWER	Reviewer name: Lee Ferguson
	Institution and Country: Boston Children's Hospital
	USA
	Competing interests: None
REVIEW REFORNED	Apr-2019
GENERAL COMMENTS	The authors report survival of infants and children admitted to PICU or general ICU in 23 hospitals in Japan that contribute to the
	JaRPAC registry over a 3-year period. This is the first multi-centre study to report survival of critically ill children in Japan in a recent era.
	In both the introduction and discussion, the authors state that there is a shortage of PICU beds in Japan. Many children are treated in general ICUs that predominantly treat adults. The manuscript would be greatly strengthened by comparing standardized mortality rates for patients cared for in PICU versus general ICU. How did the populations differ between the two? How many hospitals had PICUs versus general ICUs?
	Some specific points organized by section: Introduction
	 Page 4, line 17 – "According to an international cohort study," is then erroneously followed by 8 separate references [9-17] Page 4, line 20 – "The mortality rate for critically ill paediatric patients has not previously been reported". This should be restated – Imamura et al have reported survival in a large PICU in Osaka, Japan (Int Care Med 2012;38(4):649-654)
	 Page 4, line 31 – are you able to state the number of PICU beds available in Japan per 10,000 children and contrast this to USA/Europe? Methods
	– Page 5, line 22 Inclusion criteria. It is unclear from the statement whether patients aged >16 years admitted to a PICU were eligible to be included in the registry. If yes, was the study limited to only patients aged 16 years or less
	- Is there any external validation of the data submitted to JaRPAC to ensure accuracy of data submitted? This is not discussed in the Methods.
	 How was missing data handled in the calculation of PIM 2 scores? e.g. if patient had no arterial gas
	- What is survival? Survival to ICU discharge or hospital discharge or transfer back to local hospital?
	- PIIVIZ was first described in 2003 and has been found to
	overestimate mortality in recent era in both the UK (PICANet annual
	reports) and Japan (Int Care Med 2012;38(4):649-654). Did the
	authors use revised PIM2 equations to better estimate mortality? If
	not, this should be discussed as a limitation (particularly considering
	Imamura's study). Use of the original PIM2 equation (>15 years old)
	weakens the study findings.
	- Statistical methods - much of the data is clearly skewed (evident from the mean+/-SD of several variables presented in Table 1 e.g.
	IQR should be presented in the results and tables and non-
	(inappropriate given the skewed data)
	- Missing comma between Gl/beneto-bilien-pancreatic and
	hapmatologic/oncologic (line 14, page 6)
	Dage 6 line 25 Undear if nationts transforred to DICU from other
	hospitals considered urgent admissions?

· · ·	- Page 6, Line 16 "Cases of recovery from cardiopulmonary arrest in
	which cause could not be determined were analysed separately" but
	there is no separate presentation of this data in the results, only in
	last line of Tables 3 and 4.
	Results
-	– Page 7, line 46 - Paediatric Index of Mortality (PIM2) was 79.4 and
· · · · · · · · · · · · · · · · · · ·	48.2 This should be restated "PIM2 predicted % mortality was
	79.4% and 48.2%"
-	– Were any patients transferred from general ICU to PICU with
	EMS?
	l ables
-	- Legends for each table should be revised to aid the reader. Table
	1. Characteristics of patients that died I able 2 – Chronic
	conditions in patients that died with comorbidities.
	- Table 2 - suggest adding column for % of the 93 patients that died
	who had chronic conditions e.g. 29% had cardiovascular disease
	Discussion
	- Page 10, line 54 - "Finally, most previously healthy paediatric
	patients who had been transported from another hospital died from
	an exhibits cause, and FIVIZ was flight. Data on survival of all
	patients who were transported is not reported. The study limits itself
	actually died. Lack of presentation of mortality rate based on
	transportation limits any discussion about arguments for
	development of a national transport system in Japan
	- PIM2 scores were higher in the extrinsic cause of death group
	than the chronic condition groups 2 suggests PIM2 better at
	discrimination of death using extreme physiological data (fixed
	dilated pupils low blood pressure, high base deficit) particularly
	following cardiac arrest and less good at incorporating comorbidities
	into the model. This should be discussed more.
	- Line 31 Page 9 - "high mortality rates from unexpected trauma in
	toddlers". This data is not reported. Only 2% of patients died and I
	am uncertain how many toddlers with trauma survived. By limiting
	the results to deaths, interpretation of results is limited. How many
	toddlers had trauma and survived ICU? Multi-trauma with out-of-
	hospital cardiac arrest (as many of the patients from Table 3 and 4
	seem to have sustained) will likely have poor prognosis regardless
	of whether there is a trauma centre. No data describing whether the
	arrests were in-hospital are presented. This would be an argument
	that maybe better care could have avoided the arrests.
.	– Page 9 line 41 – "Reshaping the system". 98% of patients survived
,	with the current system. It is hard to justify reconfiguration without
	presenting data comparing survival/length of stays in adult ICUs and
	PICUs. I am unsure how many of the patients could have been
	saved given the very high PIM2 predicted mortality rates described.
.	– Page 9, line 50 – references 28,29 suggest that inter-hospital
	transfer was often correlated with admission illness severity.
	Transported patients are usually more ill and require more intensive
	care resources. The current text could be interpreted that the
	transport itself worsens the outcomes.
	What is known about the subject
	 Several typographical errors
	– Point 2 – there is larger variation in mortality rate than described
	e.g. mortality rate in PICUs in the UK in 2017 varied from 0.5-7.7%.
	The authors should state that 2-3% is overall average across
	multiple centres.
	What the study adds
.	– The study's main finding i.e. 98% survival in patients aged <=16
	years admitted to critical care in Japan should be added

REVIEWER	Reviewer name: chankramath arun
KEVIEWER	Institution and Country: Hairmyers Hospital, Hairmyers, Glasgow,
	UK
	Competing interests: NONE
REVIEW RETURNED	22-Apr-2019
GENERAL COMMENTS	Overall a reasonably well written paper, structure and conclusions
	Please address the following comments-
	Title
	1. Title needs to specify the design of the study and if possible place of study.
	Abstract
	2. Abstract- the objective statement is long and confusing. Please express them in simple statements, preferably as primary and secondary.
	3. In the methods section, please rewrite the last sentence starting with "Two patient groups" for more clarity.
	4. The results section is confusing. Please present the findings in an organized manner.
	5. There is disparity between abstract and the tables. You mention 27 subjects with cardiovascular diseases but tables 3 & 4 add to 26 only.
	6. In the last sentence of results- "Eighty three patients", please specify the group to avoid confusion.
	7. In the conclusion, you mention that major cause of death in previously healthy children was due to extrinsic causes. This is in contradiction to table 3 which says 18 of the 33 subjects died from intrinsic causes.
	Introduction
	 8. Introduction needs to be modified for better readability. The current study focus is on paediatric ICU mortality and causes for the same. Page 3, para 2 which focusses on lack of ICU beds is not fully relevant to the article considering the objectives of the current study. More importantly any data on causes of mortality in paediatric group in previous studies would be relevant in this section. 9. The rationale of the current study is not stated clearly. Please add the same in the introduction. 10. There is no mention of the probable clinical relevance or public health utility of the possible findings from this study. Such statements will inform the reader about the relevance of the current study findings. Please add them.
	Methodology 11. In the first para where the registry is described please specify how the centers were selected and also comment on the response rate. Please specify what proportion of total ICU and PICU beds in Japan were covered by the registry. If possible comment/provide indicators on the completeness of mortality data reported by the selected centers in the registry. Such information is required for assessing the generalizability of study results.
	assessing the generalizability of study results.

12. Did the study collect follow up data on those who were discharged? Did any patients expire after discharge from hospital in the first few months?
 13. How soon after admission to ICU did each patient die ? Is that data available? It might be important to determine whether deaths were due to the primary condition itself (death within first few hours) or due to secondary causes arising after hospital admission. If possible provide summary details of time from ICU admission to death overall and separately for both groups in the results section. 14. Page 5, para 1- (line 16-19) why are references 11, 25 quoted? How was CPA data obtained? 15. Paediatric Index of Mortality (PIM2)- should be described in the methods with appropriate reference.
16. In the statistical analysis section, please modify the last sentence: "The two groups were". The sentence should be about comparison, not estimation.
Results
 17. Table 1 requires modification. Some continuous variables appear to be non-normally distributed. Please check the distribution of all continuous variables. If non-normally distributed, please replace mean (SD) with Median (IQR). Avoid extrinsic causes from the list of baseline variables. Table 1 usually avoids the objectives we specify. The mortality proportion with intrinsic and extrinsic causes can be expressed in other tables. Adding an extra column for overall (both groups combined first) will make the table more informative and comprehensive. Also present p values with fixed number of decimals for uniformity. 18. In the first para of results, (Page 6 line 43) the authors mention that there were no significant differences for select baseline variables. Please provide the appropriate values and their corresponding p values to substantiate this sentence. 19. PIM2 is stated in the form of mean. Please check the distribution of the variable. If normally distributed provide the SD for both means. If not, provide median and IQR. 20. Please provide the proportion of deaths from intrinsic and extrinsic causes separately before mentioning the significance of difference. It is better to provide values in overall first, followed by two groups, and finally mention the statistical significance of the difference. This approach will avoid confusion and make things more clear.
21. Table 2 – Is this overall or just for chronic condition group? If overall, then add two columns for healthy group and chronic disease group (so 3 columns, - overall, healthy, chronic) and modify the heading of the table by removing "chronic".
Discussion
22. The discussion section needs to be modified for both structure and content. The introductory para of a discussion section is to summarize the salient points from results related to primary and secondary objective. The intermediary para are for discussing your main findings one by one relating them to other studies, mentioning the similarities and differences and providing appropriate justifications.

The last para is for concluding your discussion. Please end each intermediate discussion para with a statement summarizing the para. The current discussion section strays from an expected writing format.
23. Discussion- page 8 para2- (line 27-44) Not sure whether the comments are accurate. The study has only looked at mortality of patients in ICU, it was not designed to pick up difference in mortality between genera ICU and pediatric ICU. Not clear how recommendations related to reshaping the system can be suggested from data in the current study.
 24. Page 8 para 2 Line 28 mentions mortality differences of children admitted in general ICU versus PICU. The data regarding this difference is not collected and presented in the current study. Please refrain from discussing points outside the scope of this study. 25. Page 8 para 3- To understand whether transportation is crucial to mortality, one has to compare the transportation for once who died with once who survived in both healthy and chronic disease group. This data is not provided in the current study. If the authors can, then such a discussion is appropriate.
26. In Page 9, Line 27, the authors quote a study by Karti et al and provide two different values for admissions with chronic conditions. If these are two separate studies mentioned in Karti et al, quote both studies directly.
27. In page 9, para 3, line 46, the authors state that " In our study, the mortality rate was". The authors have not presented the mortality rate for overall, and separately for the two groups anywhere in the manuscript. Please provide the relevant values to make such a comparison. If you want to comment on the differences in the mortality rates between two groups, please report the statistical significance as well.
Conclusion
 28. Conclusion-page 10 line 42 The authors conclude that transporting paediatric patients to specialized PICU hospitals increase the risk of mortality. There is no data in the current study to compare the mortality of two groups and come to a conclusion like this. This statement needs to be removed or appropriate data needs to be added in results section with a statistical interpretation before committing the same in discussion/conclusion. 29. The current conclusion section talks less about findings from the study and more about non-specific suggestions that are not related to the study findings. Please stick to main findings of the current study and make suggestions that are extrapolated from the study findings only.
Other Comments 30. Please pay attention to the language structure. Several sentences are structured in such a way that the clarity is missing. Simple sentences that are direct and specific will enhance the readability of the manuscript.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

I mostly confine my remarks to statistical aspects of this paper.

p. 3 - I assume these data about PICU are per capita, but that should be stated explicitly.

I added to page 4 line 9-10.

p. 4 - there is a contradiction at the end of the first paragraph. I think "or ICUs" needs to be deleted.

I deleted "or ICUs"

Table 1 (and the text about it) is really the only statistical part of this paper. There are a number of errors and omissions:

For gender and extrinsic cause, the authors did not give the %ages.

I added % to each contents.

For age and length of stay, rather than mean and sd, it would be better to give median and MAD (median absolute deviation) or interquartile range. Both of these variables are clearly skew. Graphs of each, with a line for each group, would be good, as well.

I revised the data, that is clearly skew, to median and interquartile range.

In the text, the authors list several tests, but they need to say which test was done on which variable, not just "depending on their distributions".

I described what statistic test was done at the statistical analysis section.

For time of admission, referral origin and transportation, it looks like the authors tested each row. But it would probably be better to do a chi-square test - reducing 14 tests to 3.

I used chi-square test for analyzing the transportation and time of admission.

For "referral origin" I'm not sure of the utility of the analysis. "Previously healthy patients" by definition, cannot have come from a general ward or operating room. And, although I am not a pediatrician or public health professional, I'm not sure how this analysis matters.

I deleted statistic analyze of "referral origin". It does not have much meaning about this study.

For transportation, what about the 37 patients in the chronic group who came from the general ward or the operating room? They seem to have vanished in the transportation section. This needs to be made explicit.

I added the patients who came from general ward or OR in the transportation section.

Reviewer: 2

Comments to the Author

The authors report survival of infants and children admitted to PICU or general ICU in 23 hospitals in Japan that contribute to the JaRPAC registry over a 3-year period. This is the first multi-centre study to report survival of critically ill children in Japan in a recent era.

In both the introduction and discussion, the authors state that there is a shortage of PICU beds in Japan. Many children are treated in general ICUs that predominantly treat adults. The manuscript would be greatly strengthened by comparing standardized mortality rates for patients cared for in PICU versus general ICU. How did the populations differ between the two? How many hospitals had PICUs versus general ICUs?

PICU or ICU can not be distinguished from the database, so I deleted the state about comparison about PICU and ICU differences. I added the number of participating PICUs or ICUs in the METHODS, dataset section.

Some specific points organized by section:

Introduction

 Page 4, line 17 – "According to an international cohort study," is then erroneously followed by 8 separate references [9-17]

I revised the sentence. Page 3 line5-6

– Page 4, line 20 – "The mortality rate for critically ill paediatric patients has not previously been reported...". This should be restated – Imamura et al have reported survival in a large PICU in Osaka, Japan (Int Care Med 2012;38(4):649-654)

I added the report of Imamura et al. Page line 8-11

– Page 4, line 31 – are you able to state the number of PICU beds available in Japan per 10,000 children and contrast this to USA/Europe?

I deleted the discussion about PICU bed in Japan.

Methods

– Page 5, line 22 Inclusion criteria. It is unclear from the statement whether patients aged >16 years admitted to a PICU were eligible to be included in the registry. If yes, was the study limited to only patients aged 16 years or less

I described the patients age clearly in Page 4 Line 9-10.

– Is there any external validation of the data submitted to JaRPAC to ensure accuracy of data submitted? This is not discussed in the Methods.

There is no external validation, but managed by the Japanese Society for Emergency Medicine.

Page 4 Line 5-6.

- How was missing data handled in the calculation of PIM 2 scores? e.g. if patient had no arterial gas

I added to Page 5 line 14-16.

- What is survival? Survival to ICU discharge or hospital discharge or transfer back to local hospital?

I added to Page 5 line 16.

– PIM2 was first described in 2003 and has been found to overestimate mortality in recent era in both the UK (PICANet annual reports) and Japan (Int Care Med 2012;38(4):649-654). Did the authors use revised PIM2 equations to better estimate mortality? If not, this should be discussed as a limitation (particularly considering Imamura's study). Use of the original PIM2 equation (>15 years old) weakens the study findings.

I described about PIM2 limitation in discussion section.

– Statistical methods – much of the data is clearly skewed (evident from the mean+/-SD of several variables presented in Table 1 e.g. age, length of ICU stay, PIM2 predicted % mortality). Median and IQR should be presented in the results and tables and non-parametric testing undertaken. Page 7, line 20 states t-test was used (inappropriate given the skewed data)

Data is clearly skewed, so I used Median and IQR, and non-parametric testing.

- Missing comma between GI/hepato-biliary-pancreatic and haematologic/oncologic (line 14, page 6)

I added comma.

– Page 6, line 25. Unclear if patients transferred to PICU from other hospitals considered urgent admissions? I added to Page 5 Line 18-20.

– Page 6, Line 16 "Cases of recovery from cardiopulmonary arrest in which cause could not be determined were analysed separately" but there is no separate presentation of this data in the results, only in last line of Tables 3 and 4.

I deleted this sentence, because it is only in last line of Table4 and 5.

Results

Page 7, line 46 - Paediatric Index of Mortality (PIM2) was 79.4 and 48.2.... This should be restated
 "PIM2 predicted % mortality was 79.4% and 48.2%....."

I revised this sentence.

- Were any patients transferred from general ICU to PICU with EMS?

No they weren't.

Tables

– Legends for each table should be revised to aid the reader. Table 1. Characteristics of patients that died.... Table 2 – Chronic conditions in patients that died with comorbidities.

I revised the legends for each table.

Table 2 – suggest adding column for % of the 93 patients that died who had chronic conditions e.g.
 29% had cardiovascular disease

I added column for % of the 93 patients.

Discussion

– Page 10, line 54 – "Finally, most previously healthy paediatric patients who had been transported from another hospital died from an extrinsic cause, and PIM2 was high". Data on survival of all patients who were transported is not reported. The study limits itself in presenting detail on deaths only and I am unclear what proportion actually died. Lack of presentation of mortality rate based on transportation limits any discussion about arguments for development of a national transport system in Japan.

There is no date about survival of transportation, so I revised this secsion.

– PIM2 scores were higher in the extrinsic cause of death group than the chronic condition groups ? suggests PIM2 better at discrimination of death using extreme physiological data (fixed dilated pupils, low blood pressure, high base deficit) particularly following cardiac arrest and less good at incorporating comorbidities into the model. This should be discussed more. I added discussion about PIM2 predicted mortality in discussion paragraph 5.

– Line 31 Page 9 – "high mortality rates from unexpected trauma in toddlers". This data is not reported. Only 2% of patients died and I am uncertain how many toddlers with trauma survived. By limiting the results to deaths, interpretation of results is limited. How many toddlers had trauma and survived ICU? Multi-trauma with out-of-hospital cardiac arrest (as many of the patients from Table 3 and 4 seem to have sustained) will likely have poor prognosis regardless of whether there is a trauma centre. No data describing whether the arrests were in-hospital are presented. This would be an argument that maybe better care could have avoided the arrests.

I deleted "high mortality rates from unexpected trauma in toddlers", because of limited data.

– Page 9 line 41 – "Reshaping the system". 98% of patients survived with the current system. It is hard to justify reconfiguration without presenting data comparing survival/length of stays in adult ICUs and PICUs. I am unsure how many of the patients could have been saved given the very high PIM2 predicted mortality rates described.

No data about PICU and ICU comparison was available, I deleted this secsion.

– Page 9, line 50 – references 28,29 suggest that inter-hospital transfer was often correlated with admission illness severity. Transported patients are usually more ill and require more intensive care resources. The current text could be interpreted that the transport itself worsens the outcomes.

I deleted the discussion about transportation.

What is known about the subject

Several typographical errors

– Point 2 – there is larger variation in mortality rate than described e.g. mortality rate in PICUs in the UK in 2017 varied from 0.5-7.7%. The authors should state that 2-3% is overall average across multiple centres.

What the study adds

– The study's main finding i.e. 98% survival in patients aged <=16 years admitted to critical care in Japan should be added

I revised the "What is known about the subject and, What the study adds".

Reviewer: 3

Comments to the Author

Reviewers comments

Overall a reasonably well written paper, structure and conclusions need further modifications

Please address the following comments-

Title

1. Title needs to specify the design of the study and if possible place of study.

I changed the title as "Causes of death in critically ill paediatric patients in Japan: a data linkage retrospective cohort study"

Abstract

2. Abstract- the objective statement is long and confusing. Please express them in simple statements, preferably as primary and secondary.

I revised the object.

3. In the methods section, please rewrite the last sentence starting with "Two patient groups" for more clarity.

I revised the Methods section.

4. The results section is confusing. Please present the findings in an organized manner.

I revised result clearly.

5. There is disparity between abstract and the tables. You mention 27 subjects with cardiovascular diseases but tables 3 & 4 add to 26 only.

27 subjects mean is chronic condition in chronic group, it is different from final diagnosis at table 4 and 5.

6. In the last sentence of results- "Eighty three patients.....", please specify the group to avoid confusion.

I added the group.

7. In the conclusion, you mention that major cause of death in previously healthy children was due to extrinsic causes. This is in contradiction to table 3 which says 18 of the 33 subjects died from intrinsic causes.

I revised the conclusion.

Introduction

8. Introduction needs to be modified for better readability. The current study focus is on paediatric ICU mortality and causes for the same. Page 3, para 2 which focusses on lack of ICU beds is not fully relevant to the article considering the objectives of the current study. More importantly any data on causes of mortality in paediatric group in previous studies would be relevant in this section.

Lack of PICU bed is not fully relevant to the study, so I deleted the para2. I described about the causes of death in Japan.

9. The rationale of the current study is not stated clearly. Please add the same in the introduction.

I added to the para2.

10. There is no mention of the probable clinical relevance or public health utility of the possible findings from this study. Such statements will inform the reader about the relevance of the current study findings. Please add them.

I added to the para3.

Methodology

11. In the first para where the registry is described please specify how the centers were selected and also comment on the response rate. Please specify what proportion of total ICU and PICU beds in Japan were covered by the registry. If possible comment/provide indicators on the completeness of mortality data reported by the selected centers in the registry. Such information is required for assessing the generalizability of study results.

I added to the first para, about participating hosoitala and proportion of ICU and PICU bed covering.

12. Did the study collect follow up data on those who were discharged? Did any patients expire after discharge from hospital in the first few months?

This study doesn't collect data after discharge from ICU or PICU. I added in the Page 4 line10.

13. How soon after admission to ICU did each patient die ? Is that data available? It might be important to determine whether deaths were due to the primary condition itself (death within first few hours) or due to secondary causes arising after hospital admission. If possible provide summary details of time from ICU admission to death overall and separately for both groups in the results section.

The data about length of stay days in ICU or PICU is only available, so the data about time of the patients death could not be obtained.

14. Page 5, para 1- (line 16-19) why are references 11, 25 quoted? How was CPA data obtained?

CPA data is only on the last line in table 4 and 5, I revised the paragraph.

15. Paediatric Index of Mortality (PIM2)- should be described in the methods with appropriate reference.

I added in study design section, para 2.

16. In the statistical analysis section, please modify the last sentence: "The two groups were...". The sentence should be about comparison, not estimation.

I revised statistical analysis section.

Results

17. Table 1 requires modification. Some continuous variables appear to be non-normally distributed. Please check the distribution of all continuous variables. If non-normally distributed, please replace mean (SD) with Median (IQR). Avoid extrinsic causes from the list of baseline variables. Table 1 usually avoids the objectives we specify. The mortality proportion with intrinsic and extrinsic causes can be expressed in other tables. Adding an extra column for overall (both groups combined first) will make the table more informative and comprehensive. Also present p values with fixed number of decimals for uniformity.

I analysis the data by median and IQR, because the data is clearly slewed. I revised the table as comments, and add the new table about classification of disease.

18. In the first para of results, (Page 6 line 43) the authors mention that there were no significant differences for select baseline variables. Please provide the appropriate values and their corresponding p values to substantiate this sentence.

I revised the first para.

19. PIM2 is stated in the form of mean. Please check the distribution of the variable. If normally distributed provide the SD for both means. If not, provide median and IQR.

I analyzed PIM2 by median and IQR.

20. Please provide the proportion of deaths from intrinsic and extrinsic causes separately before mentioning the significance of difference. It is better to provide values in overall first, followed by two groups, and finally mention the statistical significance of the difference. This approach will avoid confusion and make things more clear.

I added the table 2 about proportion of intrinsic and extrinsic disease newly.

21. Table 2 – Is this overall or just for chronic condition group? If overall, then add two columns for healthy group and chronic disease group (so 3 columns, - overall, healthy, chronic) and modify the heading of the table by removing "chronic".

As table 2 added newly, table2 of previous manuscript is table3. It indicates only in chronic group.

Discussion

22. The discussion section needs to be modified for both structure and content. The introductory para of a discussion section is to summarize the salient points from results related to primary and secondary objective. The intermediary para are for discussing your main findings one by one relating them to other studies, mentioning the similarities and differences and providing appropriate justifications. The last para is for concluding your discussion. Please end each intermediate discussion para with a statement summarizing the para. The current discussion section strays from an expected writing format.

I revised the all over the discussion.

23. Discussion- page 8 para2- (line 27-44) Not sure whether the comments are accurate. The study has only looked at mortality of patients in ICU, it was not designed to pick up difference in mortality between genera ICU and pediatric ICU. Not clear how recommendations related to reshaping the system can be suggested from data in the current study.

I deleted this section.

24. Page 8 para 2 Line 28 mentions mortality differences of children admitted in general ICU versus PICU. The data regarding this difference is not collected and presented in the current study. Please refrain from discussing points outside the scope of this study.

I deleted this section.

25. Page 8 para 3- To understand whether transportation is crucial to mortality, one has to compare the transportation for once who died with once who survived in both healthy and chronic disease group. This data is not provided in the current study. If the authors can, then such a discussion is appropriate.

I deleted this section.

26. In Page 9, Line 27, the authors quote a study by Karti et al and provide two different values for admissions with chronic conditions. If these are two separate studies mentioned in Karti et al, quote both studies directly.

I added another reference.

27. In page 9, para 3, line 46, the authors state that " In our study, the mortality rate was....". The authors have not presented the mortality rate for overall, and separately for the two groups anywhere in the manuscript. Please provide the relevant values to make such a comparison. If you want to comment on the differences in the mortality rates between two groups, please report the statistical significance as well.

I added the relevant values in table1.

Conclusion

28. Conclusion-page 10 line 42 The authors conclude that transporting paediatric patients to specialized PICU hospitals increase the risk of mortality. There is no data in the current study to compare the mortality of two groups and come to a conclusion like this. This statement needs to be removed or appropriate data needs to be added in results section with a statistical interpretation before committing the same in discussion/conclusion.

I deleted about the section of transportation.

29. The current conclusion section talks less about findings from the study and more about nonspecific suggestions that are not related to the study findings. Please stick to main findings of the current study and make suggestions that are extrapolated from the study findings only.

I revised the conclusion section.

Other Comments

30. Please pay attention to the language structure. Several sentences are structured in such a way that the clarity is missing. Simple sentences that are direct and specific will enhance the readability of the manuscript.

I ordered my manuscript to the English emendation service.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting Competing interests: None
REVIEW RETURNED	24-May-2019

GENERAL COMMENTS	I confine my remarks to statistical aspects of this paper. These were generally simple descriptive statistics, which are fine and suit the goals of the paper. I do have a couple issues to resolve before I can recommend publication.
	p. 5, middle paragraph: How much data were missing? Substituting the normal values is not appropriate. Instead, do multiple imputation for the tests between chronic and other.
	Next para: Were other ways of dealing with admission time

examined? If you have the actual times, then I'd consider using that, perhaps with a spline, as well as another variable for weekend/weekday. Also, how were holidays dealt with?
I think table 1 could be more clearly formatted to refelct the different data that are in the text and in parentheses, but I guess it is clearer if it is closer to the text. There is also a typo - 71 for weekend daytime should probably be 7

REVIEWER	Reviewer name: Lee Ferguson Institution and Country: Boston Children's Hospital USA Competing interests: None
REVIEW RETURNED	29-May-2019

GENERAL COMMENTS	The author has addressed many of my previous comments, particularly in statistical analysis of results and focus of the study. Further suggestions to improve readability:
	Introduction - line 54 - I am not sure how indication of death profiles will improve mortality rate. Suggest delete or restate
	Results: Page 6, Line 44 - 6066 survivors +126 deaths = total of 6192 but line 1 of results states 6199 patients in database Page 6, Line 50 - add % in brackets e.g. "Among the patients who were discharged, 3,605 patients (58%) belonged to the chronic condition group and 2,594 patients (42%)" Page 6, Line 54 - Add in percentage & P value from chi square test "Thirty-three children without a chronic illness (1.3%) and 93 chronically ill patients (2.6%) died (P<0.001)" Page 6, Line 56 - this data is presented in the Table 1. Rather than duplicate, suggest stating "There were no significant differences in age, gender, admission urgency, or median length of ICU or PICU stay between the two groups (Table 1)." Page 7, Line 8 - median PIM2 % mortalities are in patients that died. This should be stated. It would be helpful to have PIM2 predicted mortalities of all admissions by chronic group/no chronic illness group if available. Page 7, Line 17 - sentence does not make sense Page 7, Line 21 - suggest simplify to "difference in extrinsic disease (45% versus 11%, p<0.01) between the two groups."
	Discussion: Page 8, line 14 - "This is the first multicenter" sentence would be best placed at the start of the discussion Page 8, line 21 - suggest change to "and our findings are consistent to other reports" Page 9, line 46 - Stated incorrectly. PIM2 predicted % mortality of patients that died was higher in children without a chronic illness. Data for overall PIM2 predicted % mortality for all admissions to ICU/PICU by chronic illness/no chronic illness is not presented. Table 1 - suggest relabelling for clarity Title - change to: Characteristics of patients that died in ICU or PICU "PIM2 (%)" should be PIM2 predicted mortality (%) "p-values" should be p-value "Total" should be "All deaths"

Replace "Dead case, n" with Characteristics
Table 2 - "Dead case" should be labelled as Cause of death p-values should not be plural (only one value stated) What is the p-value? Why not chi-squared of extrinsic vs intrinsic across both groups?
Table 4 - Suggest title: "Cause of death in patients without chronic illness" Change "Recovery from CPA" to "Cardiac arrest". Were these pre- admission or in ICU? This would be interesting to the reader. Change "Unknown CPA" to "Unknown"

REVIEWER	Reviewer name: Chankramath arun Institution and Country: Hairmyers Hospital Hairmyers, Glasgow Competing interests: None
REVIEW RETURNED	10-Jun-2019

GENERAL COMMENTS	All queries have been addressed satisfactorily, hence happy for it to
	go ahead

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

I confine my remarks to statistical aspects of this paper. These were generally simple descriptive statistics, which are fine and suit the goals of the paper. I do have a couple issues to resolve before I can recommend publication.

p. 5, middle paragraph: How much data were missing? Substituting the normal values is not appropriate. Instead, do multiple imputation for the tests between chronic and other.

There was no data about how much data were missing. PIM2 can calculate without missing data. I revised the sentence. Page 5 line 14-16.

Next para: Were other ways of dealing with admission time examined? If you have the actual times, then I'd consider using that, perhaps with a spline, as well as another variable for weekend/weekday. Also, how were holidays dealt with?

There is no data about actual time. I added the sentence. Page 5 line 22.

I think table 1 could be more clearly formatted to refelct the different data that are in the text and in parentheses, but I guess it is clearer if it is closer to the text. There is also a typo - 71 for weekend daytime should probably be 7

I revise the table 1.

Peter Flom

Reviewer: 2

Comments to the Author

The author has addressed many of my previous comments, particularly in statistical analysis of results and focus of the study. Further suggestions to improve readability:

Introduction - line 54 - I am not sure how indication of death profiles will improve mortality rate. Suggest delete or restate

I deleted this sentence.

Results:

Page 6, Line 44 - 6066 survivors +126 deaths = total of 6192 but line 1 of results states 6199 patients in database

I revised 6,066 to 6,073. Page 6 line 23.

Page 6, Line 50 - add % in brackets e.g. "Among the patients who were discharged, 3,605 patients (58%) belonged to the chronic condition group and 2,594 patients (42%)"

I added percentage. Page 6 line 24-25.

Page 6, Line 54 - Add in percentage & P value from chi square test "Thirty-three children without a chronic illness (1.3%) and 93 chronically ill patients (2.6%) died (P<0.001)"

I added percentage and P value. Page 6 line 27.

Page 6, Line 56 - this data is presented in the Table 1. Rather than duplicate, suggest stating "There were no significant differences in age, gender, admission urgency, or median length of ICU or PICU stay between the two groups (Table 1)."

I revised the sentence. Page 6 line27 – Page 7 line1.

Page 7, Line 8 - median PIM2 % mortalities are in patients that died. This should be stated. It would be helpful to have PIM2 predicted mortalities of all admissions by chronic group/no chronic illness group if available.

I added sentence. Page 7 line 1-4.

Page 7, Line 17 - sentence does not make sense

I deleted the sentence.

Page 7, Line 21 - suggest simplify to "....difference in extrinsic disease (45% versus 11%, p<0.01) between the two groups."

I revised the sentence. Page 7 line 10.

Discussion:

Page 8, line 14 - "This is the first multicenter...." sentence would be best placed at the start of the discussion

This sentence is changed to place at the start of the discussion. Page8 line 2-3.

Page 8, line 21 - suggest change to "and our findings are consistent to other reports"

I revised the sentence. Page 8 line 11-12.

Page 9, line 46 - Stated incorrectly. PIM2 predicted % mortality of patients that died was higher in children without a chronic illness. Data for overall PIM2 predicted % mortality for all admissions to ICU/PICU by chronic illness/no chronic illness is not presented.

I revised the sentence. Page 9 line 24-25.

Table 1 - suggest relabelling for clarity

Title - change to: Characteristics of patients that died in ICU or PICU

"PIM2 (%)" should be PIM2 predicted mortality (%)

"p-values" should be p-value

"Total" should be "All deaths"

Replace "Dead case, n" with Characteristics

I revised the table 1 along to the comments.

Table 2 - "Dead case" should be labelled as Cause of death

p-values should not be plural (only one value stated)

What is the p-value? Why not chi-squared of extrinsic vs intrinsic across both groups?

I revised the table2.

Table 4 - Suggest title: "Cause of death in patients without chronic illness"

Change "Recovery from CPA" to "Cardiac arrest". Were these pre-admission or in ICU? This would be interesting to the reader.

Change "Unknown CPA" to "Unknown"

I revise the table 4 along to the comments.

Reviewer: 3

Comments to the Author

All queries have been addressed satisfactorily, hence happy for it to go ahead

Thank you for revising my manuscript.

VERSION 3 – REVIEW

REVIEWER	Reviewer name: Peter Flom Institution and Country: Peter Flom Consulting, USA
	Competing interests: None
REVIEW RETURNED	20-Jun-2019

GENERAL COMMENTS	The authors have addressed my concerns and I now recommend
	publication

REVIEWER	Reviewer name: Lee Ferguson
	Institution and Country: Boston Children's Hospital, USA
	Competing interests: None
REVIEW RETURNED	30-Jun-2019

GENERAL COMMENTS	 Some minor points to improve the manuscript: Table 4 – CPA abbreviation not needed in footnote as no longer used in table Page 9, line 50 – add "mortality" – "In this study, PIM 2 predicted % mortality in patients who died" Abstract line 13 – add "who died" to end of sentence Conclusion – page 10, line 51 – "the mortality rate due extrinsic causes was higher in the children without a chronic illness than in the chronic condition group" is not supported by the data. Suggest rephrase "the proportion of deaths due to extrinisic causes was higher in children without chronic illness". Similar change should be made to conclusions in abstract What this study adds, point 2: Better stated as:

"The proportion of deaths due to extrinsic disease was higher in
children without a chronic illness"
- What is known about the subject, Point 1: Survival spelt incorrectly

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Thank you for your recommendation about publication of my article.

Reviewer: 2

Comments to the Author

Some minor points to improve the manuscript:

- Table 4 - CPA abbreviation not needed in footnote as no longer used in table

I deleted CPA abbreviation.

- Page 9, line 50 – add "mortality" – "In this study, PIM 2 predicted % mortality in patients who died....."

I added "mortality" to the sentence.

- Abstract line 13 - add "who died" to end of sentence

I added the "who died" to end of sentence.

- Conclusion – page 10, line 51 – "the mortality rate due extrinsic causes was higher in the children without a chronic illness than in the chronic condition group" is not supported by the data. Suggest rephrase "the proportion of deaths due to extrinisic causes was higher in children without chronic illness". Similar change should be made to conclusions in abstract.

I revised the sentence.

- What this study adds, point 2: Better stated as: "The proportion of deaths due to extrinsic disease was higher in children without a chronic illness"

I revised the sentence.

- What is known about the subject, Point 1: Survival spelt incorrectly

I corrected the word.