PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology and outcome of adult out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study
AUTHORS	Kitamura, Tetsuhisa; Kiyohara, Kosuke; Sakai, Tomohiko; Iwami, Taku; Nishiyama, Chika; Kajino, Kentaro; Nishiuchi, Tatsuya; Hayashi, Yasuyuki; Katayama, Yusuke; Yoshiya, Kazuhisa; Shimazu, Takeshi

VERSION 1 - REVIEW

REVIEWER	Hideo Inaba Department of emergency medical science, Kanazawa University Graduate school of Medicine
REVIEW RETURNED	08-Sep-2014

GENERAL COMMENTS	The reasons why the authors exclude the OHCA patients aged <20 were not clearly given. Many similar papers have been published from Osaka project. It is not clear what is the new finding in this study. Limitation Exlusion of OHCA patients aged <20 should be discussed. #1 Page 8 Line 4-7 The reasons why the authors exclude the OHCA patients aged <20 were not clearly given. #2 Statistical analysis In multiple regression, any indicator for the fitness of model should be given.

REVIEWER	Dr Janet Bray Monash University, Australia I am a Research Fellow with the Australian Resuscitation Outcomes Consortium and published research with OHCA registries.
REVIEW RETURNED	16-Sep-2014

GENERAL COMMENTS	This study used an Utstein-based registry to study survival and

related factors in OHCA of non-cardiac origin in an area of Japan. The study found no improvement in survival in this group of patients and identified plausible related factors. The authors are to be commended on their follow-up to obtain neurological outcomes. I have the following comments:

1. More information is need on the classification of "non-cardiac origin". The paper states that this was done by a physician but does not state what information was available to them to make this decision. For example –did they have hospital medical notes or coroners reports. If this decision was made based on EMS reports it is a "presumed" diagnosis (particularly for internal causes) and this should be made clear in the title, abstract and throughout the paper.

2. Is the classification cerebrovascular diseases - Strokes? CVD is an out-of-date term and stroke should be used.

3. The current survival model includes all non-cardiac OHCA. I think it would be more relevant to stratify your analysis by internal and external causes. Related factors are likely to be different for these two groupings (including bystander CPR).

4. How was asphyxia chosen as the reference group? What is the value in the comparative ORs?

5. Did you check for an interaction between age and ADL?

6. Why did your use VF yes/no in your model and not actual rhythm?

7. Why did you include intravenous fluid in your model? Isn't this likely interact with the cause of arrest or illness severity?

8. Why did you enter year as a continuous variable? It would be good to know either the unadjusted annual survival rates (could these be added to Table 1) or use year as a categorical variable in your model. Particularly given you indicate an improvement in some years in your discussion.

9. How do your rates of external OHCAs compare to other published studies? Are there some external causes that are more common in your region?

10. As highlighted in your methods, nearly all OHCA received an attempted resuscitation in your region. Thus your attempted resuscitation rates is extremely high at 92%. Thus your findings are almost comparable to other regions entire OHCA cohorts and not just those who receive an attempted resuscitated. This high rate in your region may explain some of the findings in your model, such as the lack of impact of bystander CPR. Given your sample, I would suggest you provide discussion around this and also report your bystander CPR rates for witnessed arrests.

11. The third paragraph of the introduction should be moved to the methods.

12. Page 19 line 7-7 "cardiac non-cardiac origin" ?

Models may require adjustment based on my comments

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1: Dr. Hideo Inaba

Thank you for your important comments. Our responses to your queries follow.

The reasons why the authors exclude the OHCA patients aged <20 were not clearly given.

Some preceding reports showed that characteristics and outcomes from OHCAs differed between children and adults (Nitta M, et al. Pediatrics 2011;128:812 and Atkins DL, et al. Circulation 2009;119:1484). Therfore, this study focused only on adults with non-cardiac OHCAs. In addition, the Osaka Utstein Project already published a report on epidemiology and outcomes of pediatric OHCAs (Nitta M, et al. Pediatrics 2011;128:812).
However, according to the Reviewer's suggestions, we added the sentence in the Methods as follows (Page 8 Line 7); "In this study, we excluded pediatric OHCA patients because characteristics and outcomes from OHCAs differed between children and adults.16,17"

Many similar papers have been published from Osaka project. It is not clear what is the new finding in this study.

In a lot of previous reports from the Osaka Utstein Project, we have focused on bystander-witnessed adult OHCAs with cardiac origin based on the recommendation of Utstein reporting gidelines. However, 20-40% of adult OHCAs were reportedly of non-cardiac origin, and the epidemiological characteristics have not been sufficiently investigated as much as those of OHCA with cardiac origin. Thereofre, we consider that the evaluation of characteristics, trends, and outcomes by detailed non-cardiac cause and understanding the factors associated with the outcomes are needed to improve the survival after OHCAs with non-cardiac origin, as mentioned in the Introduction.
As mentioned in the Discussion, this study showed that one-month survival after OHCAs with non-cardiac origin was poor and the survival trends did not improve year-by-year, and the survivals differed by detailed non-cardiac origin. Thus, these findings describing the actual situation regarding the incidence and outcome of OHCAs with non-cardiac origin is of help to improve the survival as basic data.

Limitation
Exlusion of OHCA patients aged <20 should be discussed.

Since we added the sentence that we excluded pediatric OHCA patients in the Methods, we consider that the exclusion of pediatric OHCA patients is exempted from discussion in this study.

#1 Page 8 Line 4-7
Why did you excluded OHCA patients aged <20?

Please see above.

#2 Page 13, Line 3-10
Please show any indicator for the fitness of this model. In this the best model?

In a multivariate analysis, the selection of models or factors is different ways for the study aim. As mentioned in the Methods, the aim of multiple logistic regression analysis in this study was to assess various factors associated with one-month survival and neurological favorable outcome, and was not to provide the best statistical model. Therefore, in our model, we selected various factors that were biologically essential and considered to be associated with clinical outcomes were taken in the multivariable analyses as potential confounders.

#3 Many papers have been published from the Osaka Project. What is the new finding?

Please see above.

Response to Reviewer 2: Dr. Janet Bray

This study used an Utstein-based registry to study survival and related factors in OHCA of non-cardiac origin in an area of Japan. The study found no improvement in survival in this group of patients and identified plausible related factors. The authors are to be commended on their follow-up to obtain neurological outcomes. I have the following comments:

Thank you for your thorough reviews. Our responses to your queries follow.

1. More information is need on the classification of "non-cardiac origin". The paper states that this was done by a physician but does not state what information was available to them to make this decision. For example –did they have hospital medical notes or coroners reports. If this decision was made based on EMS reports it is a "presumed" diagnosis (particularly for internal causes) and this should be made clear in the title, abstract and throughout the paper.

The classification of non-cardiac origin was based on hospital medical records as the Reviewer pointed out. We revised the sentence in the Methods as follows (Page 8 Line 11); "In this study, the arrests were classified into those of presumed cardiac origin and non-cardiac origin, the latter resulting from external causes, respiratory diseases, malignant tumors, strokes, and any other non-cardiac causes based on hospital medical records."

2. Is the classification cerebrovascular diseases - Strokes? CVD is an out-of-date term and stroke should be used.

We changed the term "cerebrovascular diseases" to "strokes" in the Text, Tables, and Figure.

3. The current survival model includes all non-cardiac OHCA. I think it would be more relevant to stratify your analysis by internal and external causes. Related factors are likely to be different for these two groupings (including bystander CPR).

In line with the Reviewer's suggestions, we added a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes. Our study aimed to assess factors associated with one-month survival and neurological favorable outcome in whole OHCAs with non-cardiac origin, and this analysis was added as the Sapplemental Table. Please see Supplemental Table. In this analysis, we did not assess factors associated with neurological favorable outcome because the number of surviors with better neurological outcome after dividing the two groups was small.

According to these changes, we added the following sentences; "In addition, we conducted a multivariate analysis of one-month survival from OHCAs with non-cardiac origin after dividing the two groups: internal (respiratory diseases, malignant tumors, and strokes) and external (asphyxia, hanging, fall, drowning, traffic injury, and drug overuse) causes." in the Methods (Page 13 Line 13) and "Subgroup analyses after dividing the two groups (internal and external causes) are shown in Supplemental Table. As for internal causes, arrests witnessed by bystanders (AOR 2.86, 95% CI 1.99-4.11), VF as first documented rhythm (AOR 2.35, 95% CI 1.30-4.24), and public places (AOR 2.01, 95% CI 1.21-3.36) were associated with improving outcome. As for external causes, adults (AOR 1.51, 95% CI 1.17-1.96), arrests witnessed by bystanders (AOR 5.03, 95% CI 3.71-6.81), good ADL before arrests (AOR 1.34, 95% CI 1.08-1.67), intravenous fluid (AOR 1.69, 95% CI 1.27-2.25), and early EMS response time (AOR for one-increment of minute 0.93, 95% CI 0.90-0.96) were associated with improving outcome." in the Results (Page 17 Line 17).

4. How was asphyxia chosen as the reference group? What is the value in the comparative ORs?

Although the selection of a factor as the reference in the multivariable model differed by the study aim, we slected the factor "asphyxia" as the reference in this study because the number of sample and better otucome was most frequent.

5. Did you check for an interaction between age and ADL?

We investigated an interaction between age and ADL in outcomes. Their P values were 0.126 in one-month survival and 0.358 in neurologically favorable outcome, and the interaction was not statistically significant.

6. Why did your use VF yes/no in your model and not actual rhythm?

Like a lot of peceding studies, we consider that dividing the first documented rhythm into the two groups: VF (shockable) or non-VF (non-shockable) is important in the multivariate analysis, and this classification is, therefore, acceptable for the Journal Readers.

7. Why did you include intravenous fluid in your model? Isn't this likely interact with the cause of arrest or illness severity?

In the EMS systems of Japan, prehospital intravenous fluid was one of advanced life supports attempted by trained EMS personnel for OHCA patients who did not respond basic life support irrespective of the cause of arrest or illness severity during the study period. Therefore, intravenous

fluid dose not interact with them and we incorporated it into the multivariate analysis in order to assess effects of advanced life supports on non-cardiac OHCAs.

8. Why did you enter year as a continuous variable? It would be good to know either the unadjusted annual survival rates (could these be added to Table 1) or use year as a categorical variable in your model. Particularly given you indicate an improvement in some years in your discussion.

In line with the Reviewe's suggestions, we added the unadjusted one-month survival rate in Table 1. Please see revised Table 1.
According to these changes, we revised the setntence in the Methods as follows (Page 13 Line 1); "Poisson regression models for the trends in the incidence and one-month survival rate were used." and added the following sentences in the Results (Page 15 Line 17); "The unadjusted one-month survival rates by non-cardiac cause were almost stable during the study period."

9. How do your rates of external OHCAs compare to other published studies? Are there some external causes that are more common in your region?

We consider that comparison of external OHCA incidence and outcome with that in other areas is important as the Reviewer pointed out, and added the sentences in the Discussion as follows (Page 20 Line 8); "For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile. Thus, there were regional variations on the incidence and outcome from OHCAs with external causes,22,23 and the countermeasures would differ by regions."

10. As highlighted in your methods, nearly all OHCA received an attempted resuscitation in your region. Thus your attempted resuscitation rates is extremely high at 92%. Thus your findings are almost comparable to other regions entire OHCA cohorts and not just those who receive an attempted resuscitated. This high rate in your region may explain some of the findings in your model, such as the lack of impact of bystander CPR. Given your sample, I would suggest you provide discussion around this and also report your bystander CPR rates for witnessed arrests.

Thank you for your important suggestions. In line with the Reviewer's suggestions, we added the sentences in the Discussion as follows (Page 21 Line 13); "In addition, attempted resuscitation rates in our area was exceedingly higher at 92% compared with those in western countirs,22,26 which might be also one of the possible explanations for the lack of impact of bystander CPR in our multivariate model."
Furthermore, we added the sentence about the proportion of bystander CPR in the Results as follows (Page 16 Line 14); "The proportion of bystander chest compression-only CPR and conventional CPR with rescue breathing was 23.2% and 13.1% in whole OHCAs with non-cardiac origin, and 22.1% and 14.3% in bystander-witnessed OHCAs."

11. The third paragraph of the introduction should be moved to the methods.

In our reports including this study, we always described the concept of our cohort and the aim of study in the final paragraph of the Introduction. We believe that this would be very important

because the Journal readers can catch up our cohort in the Introduction. However, if the Editor prefers to move the sentence, we will do so.

12. Page 19 line 7-7 "cardiac non-cardiac origin" ?

Sorry for our mistakes. We deleted the word "cardiac." (Page 21 Line 13)

Models may require adjustment based on my comments.

In line with this Reviewer's comments, we re-analized our models as mentioned above.

VERSION 2 – REVIEW

REVIEWER	Hideo Inaba Department of Emergency Medical Science, Kanazawa University Graduate school of Medicine
REVIEW RETURNED	18-Oct-2014

GENERAL COMMENTS	# The reason why the authors excluded the pedediatric OHCAs (under 20y) is still unclear. OHCAs of non-cardiac etiology are very common in the population age of <35y or <30y. Some preceding reports showed that characteristics and outcomes from OHCAs differed between children and adults. However, the definition of child or pediatric OHCAs differed among the reports. # Otherwise, the title and abstract should be changed for readers to understand that this study focused adult non-cardiac OHCAs.

REVIEWER	Dr Janet Bray Monash University, Australia
REVIEW RETURNED	29-Oct-2014

GENERAL COMMENTS	The authors have addressed all previous comments. The English throughout the paper could use editing and the subsequent analysis performed has raised a few more minor questions: 1. Large registries such as this usually have some missing data. Please describe rates of missing data for key variables and how this was handled in the statistical modelling. 2. The abstract states: "In a multivariate analysis, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with **cardiac** origin." Please change to

"**non-cardiac origin'**.

3. Why does the text of the abstract and results not refer to the statistical significance of age in your models?
4. The discussion around bystander CPR requires some revision. I suggest a section of this paragraph is changed to: Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin **in our region** might be related to the significantly high rates of attempted EMS resuscitation in Japan compared with those in western **countries**.22,26 However, as recommended in the CPR guidelines,1-4 bystander CPR plays a key role in the "chain of survival" and increasing the proportion of bystander CPR for OHCA patients is important.
5. The insertion of the Melbourne paper to the discussion does not read well and requires revision. You need to bring in regional differences before the example.
6. Spelling error: "Sapplemental Table"
7. Spelling error: "rescue brething" in Supplemental Table.

VERSION 2 – AUTHOR RESPONSE

Response to Reviewer 1: Dr. Hideo Inaba

The reason why the authors excluded the pediatric OHCAs (under 20y) is still unclear. OHCAs of non-cardiac etiology are very common in the population age of <35y or <30y. Some preceding reports showed that characteristics and outcomes from OHCAs differed between children and adults. However, the definition of child or pediatric OHCAs differed among the reports.
Otherwise, the title and abstract should be changed for readers to understand that this study focused adult non-cardiac OHCAs.

Thank you for your comments. Although the definition of children or pediatric OHCAs differed among the reports as the Reviewer pointed out, our study focused on epidemiology and outcome among adult patients aged >=20 years old with non-cardiac OHCAs. In line with the Reviewer's suggestion, we revised the Title (Page 1 Line 1) and Participants in the Abstract (Page 3 Line 7) as follows; "Epidemiology and outcome of adult out-of-hospital cardiac arrest with non-cardiac origin in Osaka: a population-based study." and "14,164 adult patients aged >= 20 years old with OHCAs due to non-cardiac origin who were resuscitated by emergency-medical-service personnel or bystanders."

Response to Reviewer 2: Dr. Janet Bray

The authors have addressed all previous comments. The English throughout the paper could use editing and the subsequent analysis performed has raised a few more minor questions:

Thank you for your reviews. We asked an English language editing service to eliminate some grammatical errors and to conform to correct scientific English.

1. Large registries such as this usually have some missing data. Please describe rates of missing data for key variables and how this was handled in the statistical modelling.

As the Reviewer pointed out, our study had some missing data on characteristics and outcomes of non-cardiac OHCAs, but the numbers were very small. We added information on missing data in a footnote of Tables 2 and 4. Please see them. Furthermore, we added the following sentence in the Results (Page 15 Line 11); "We could not obtain information on one-month survival and neurological status for 7 (0.05%) among 14,164 eligible victims."

2. The abstract states: "In a multivariate analysis, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with cardiac origin." Please change to "non-cardiac origin'.

Sorry for our careless mistake. We corrected it (Page 4 Line 5).

3. Why does the text of the abstract and results not refer to the statistical significance of age in your models?

In line with the Reviewer's suggestion, we revised the sentences in the Results of the Abstract and Text as follows; "In a multivariate analysis, adults aged <65 years old, arrests witnessed by bystanders, good activities of daily living before arrests, ventricular fibrillation arrests, public places, intravenous fluid, and early emergency-medical-service response time were significant predictors for one-month outcome after OHCAs with non-cardiac origin (Page 4 Line 3)." and "In one-month survival, adults aged <65 years old (AOR 1.36, 95% CI 1.12-1.65), arrests witnessed by bystanders (AOR 4.13, 95% CI 3.35-5.09), good ADL before arrests (AOR 1.23, 95% CI 1.03-1.47), VF as first documented rhythm (AOR 2.04, 95% CI 1.42-2.92), public places (AOR 1.45, 95% CI 1.10-1.91), intravenous fluid (AOR 1.45, 95% CI 1.14-1.84), and early EMS response time (AOR for one-increment of minute 0.92, 95% CI 0.90-.095) were associated with improving outcome (Page 17 Line 3)."

4. The discussion around bystander CPR requires some revision. I suggest a section of this paragraph is changed to: Considering these results, the effectiveness of bystander CPR on OHCAs with non-cardiac origin in our region might be related to the significantly high rates of attempted EMS resuscitation in Japan compared with those in western countries.22,26 However, as recommended in the CPR guidelines,1-4 bystander CPR plays a key role in the "chain of survival" and increasing the proportion of bystander CPR for OHCA patients is important.

Thank you for your revision. Done as requested (Page 21 Line 12).

5. The insertion of the Melbourne paper to the discussion does not read well and requires revision. You need to bring in regional differences before the example.

In line with the Reviewer's suggestion, we revised the sentence in the Discussion as follows (Page 20 Line 6); "On the other hand, the incidence rates of OHCAs with external causes in our region increased and the outcomes after OHCAs with external causes excluding asphyxia were miserable. However, there were regional variations on the incidence and outcome from OHCAs with external causes.[22,23] For example, external OHCAs due to trauma, drug overdose, or hanging in metropolitan area of Australia were more common and the survivals from traumatic and hanging-associated OHCAs were not always futile, and the countermeasures would, therefore, differ by regions. Most importantly, more efforts should focus on prevention of OHCAs with external causes because many of them are preventable.[1-4]"

6. Spelling error: "Sapplemental Table"

Sorry for our careless mistake. We corrected it (Supplemental Table).

7. Spelling error: "rescue brething" in Supplemental Table.

Sorry for our careless mistake. We corrected it (Supplemental Table).