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OPEN PEER REVIEW

Application of Mixture Cure Models in Determining the Survival of Patients with Cervical Cancer

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About this report

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1 Original submission

1 comment · 11 Nov 2019

Editor-in-Chief

MAJOR REVISION 11 Nov 2019

Dear Author,
Thank you for submitting your manuscript to IJCM. Please revise your manuscript according to the associate editor's comments. In addition, please structure the abstract of your manuscript according to the instructions on the IJCM website.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

With greetings and respect to the dear colleagues and respected reviewers of the esteemed journal of Shahid Beheshti University

Based on the comments of the respected reviewers, the article was revised in collaboration with the research team, and the following items were corrected in the text with blue highlights; explanations regarding the calculation of the sample size in the model used are also attached.

With thanks

Explanations related to the sample size

Suppose S(x) is the probability of survival up to time x, assuming that the distribution is exponential

$$S(x) = \exp(-\lambda x) \quad (3\text{-}32)$$

The hazard function at time x is:

$$h(x) = \lambda = -Ln\, S(x) \quad (3\text{-}33)$$

If $\hat{\lambda}$ is the estimate λ, the estimate being the number of deaths that occurred in the studied sample divided by the length of follow-up time, then $\hat{\lambda}$ has a normal distribution with mean λ and variance $\frac{\Phi(\lambda)}{n}$, where:

$$\Phi(\lambda) = \lambda^2 \left[1 - \frac{e^{-\lambda(T-T_0)} - e^{-\lambda T}}{\lambda T_0}\right]^{-1} \quad (3\text{-}34)$$

where T_0 is the start time of censoring and T is the end time of follow-up. Therefore, the sample size for confidence 1-α and precision d is:

$$n = \frac{(Z^{\square}_{1-\frac{\alpha}{2}})^2 \Phi(\lambda)}{d^2} \quad (3\text{-}35)$$

According to preliminary studies, during the 80 months examined, the incidence of death was about 0.006 (6 per thousand people per month). Therefore, to estimate survival with a maximum error of 2 per thousand (0.002) and 95 percent confidence, a sample of 115 people will be adequate for the study. In this calculation, the start time of censoring

was considered to be about 40 months, a value obtained from .the preliminary study

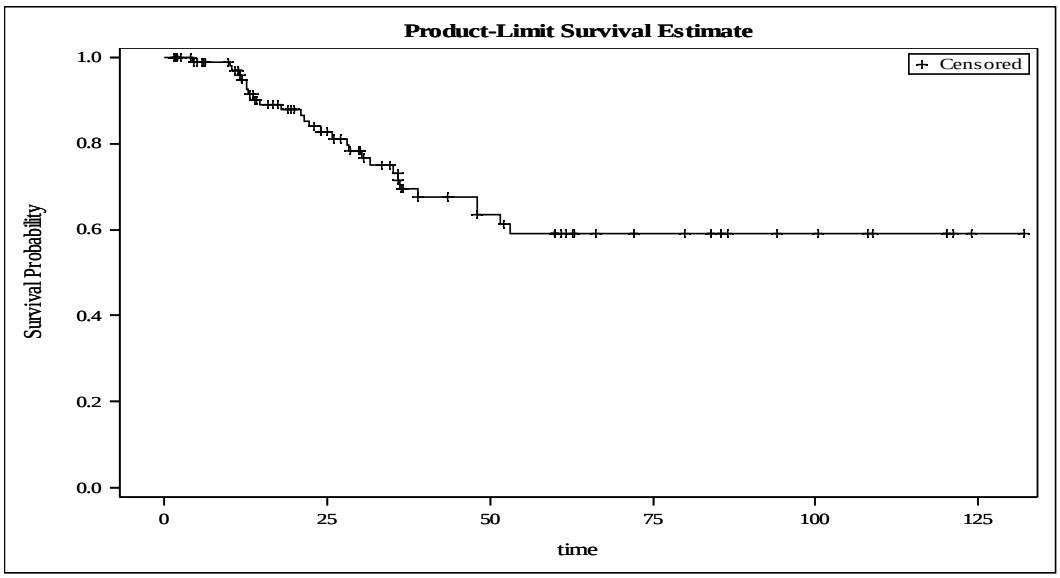
$$\lambda = \widehat{H}(80) = -\ln \hat{S}(80) = ¿\, 0.006\, ¿$$
$$\Phi = 0.006^2 \left[1 - \frac{e^{-0.006(80-40)} - e^{-0.006(80)}}{0.006(40)} \right]^{-1} = 0.00011 \qquad (3\text{-}36)$$
$$n = \frac{(1.96)^2 (0.00011)}{(0.002)^2} = 115$$

Using this formula, the sample size is appropriate for a cure model; also, in reviewing previous literature and articles, the sample size was at this level and .even lower

For reporting the cure percentage and whether the cure model can be used or not

One of the common methods for examining immune (cured) individuals is the use of the Kaplan-Meier plot; if immune individuals are present, the Kaplan-Meier plot becomes a horizontal line before reaching zero (13). Graph 1 .indicates the presence of immune individuals in the studied data

Graph 1



One of the most important assumptions for using the cure model is examining the cure fraction. The observed results show that the proportion of immune individuals in the study is 40%, which is a considerable and significant proportion, p-value=0.05. (Table 2)

Table 2- Results of examining the presence of immune individuals in the cure model

p-value	Confidence interval		Proportion of immune individuals	
	Lower limit	Upper limit		
05/0	29/0	25/3	40/0	Cure Cox model

This article is not a purely statistical article in which we develop a new statistical model; it is an applied article that compared several models, and we have introduced the best model and statistical distribution for these cancer data

While formatting the article according to the journal's structure, the language .of the article was revised again

Acknowledgments were added and the approved project code was written. The authors' contributions were entered in detail

Acknowledgments

This study was extracted from approved project with code 1394-0--63-1807 and the authors would like to thank the deputy of University research of Urmia for financial support, .cooperation of health providers who participated in the completion of the sampling stages

The authors' contributions were entered in detail

Footnotes

Conflict of interests was added and the ethics code of the project was written. Funding was entered in detail

.**Conflict of Interests**: There are no conflicts of interest between authors

Ethical Approval: The Ethical Review Committee of Urmia University of Medical Sciences .approved this study (Ir.umsu.rec.1394.361)

Funding/Support: The study was supported in part by grant (Number: 1807) from Urmia .University of Medical Sciences

.**Informed Consent**: Informed consent was taken from patients

:The references were entered according to the journal's format with DOI

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2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear colleagues,

After appreciating you all for valuable comment, here are the all changes.
Actually this paper is extracted of an approved project in our university and published its first article in the "Asian Pacific journal of cancer prevention" which is PubMed and Scopus like your valuable journal entitled" Ten years' survival in patients with cervical cancer and related factors in West Azerbaijan Province: Using of cox proportion hazard model". Additionally, various articles using cure model was done and published with less same size. In this paper 109 patients were eligible after assessing inclusion criteria that is why before 2004 either the patients' information was not recorded or it was not complete and they could not be used in the model. Then we believe that sample size is enough. However other comments behalf of dear authors can help us in this regard. So many thanks.

1. "Meier" was replaced with "Mayer".

The following comment was reposed consequently.

In calculation of sample size, d (0.002) is great in contrast to standard deviation (0.006). Although, the exponential distribution has not been assumed in analysis, for sample size calculation this distribution has been assumed. The scenario and duration of follow up was not defined. What time has been defined as "the end of the study"? Why has been performed parametric methods (Weibull, log-normal and log-logistic) to determine the short-term survival and the Logit's function was also used to determine the long-term survival. Where and why has cox cure model been used? Explain it.

2. In the usual methods of survival analysis, it is assumed that all individuals in the study community are prone to the desired outcome, while there are times when some members of the community are immune to the event and do not experience it for the rest of their lives. These people are called cured or improved groups.

Therefore, in this case, the basic assumption of the usual methods of survival analysis is invalidated, and to study such a community, which consists of two sub-groups, talented and safe, survival analysis methods known as cure models should be used. In Cox's proportionate risk model, one of the assumptions is that all those studied will gradually experience the desired outcome by the end of the study. If there are immunosuppressed people in our study, the use of the Cox method is not appropriate, as one of its main assumptions has been distorted. For this reason, it is necessary to use models that do not require this default, which are known as cure models. On the other hand, in studies where the target population is composed of two groups of susceptible and non-susceptible or cure to death due to cancer, it is better to use the cure model,

because in this method we will be able to analyze the curability and distribution of the time of the event, ie the death caused by the disease, for the susceptible individuals separately.

Reference

Maller RA, Zhou X. Survival analysis with long-term survivors: John Wiley & Sons; 1996.

The following texts maybe help us to transfer our concept.

Extra description

In survival analysis, it is usually assumed that all individuals gradually experienced the event of interest until the end of the observation period (1). In some situations, a substantial proportion of individuals do not experience the event under the study at the end of follow-up time (2). Under this circumstance, the population consists of two groups: the group of individuals who do not experience the event of interest (or long-term survivors) and the group of patients who are susceptible (or non-cured) to the disease (3). In such a situation, standard survival analysis is not a proper method because of increases in a number of censoring at the end of the follow-up period, which does not account for the possibility of long-term survivors (1). In order to confirm that a considerable number of cases do not eventually experience the event of interest until the end of the follow-up time, the Kaplan-Meier survival plot can be a useful tool to reveal whether the plot reached zero with the current amount of follow-up time; so, a significant number of cases is cured and also it appears that there is a considerable cure fraction in dataset (4). In the case of high cure fraction, Cox regression model will lead to bias estimates. Cure models allow us to build a model, which can determine risk factors which have had a significant effect on survival of cured and uncured patients (4). Since a proportion of individuals will survive from the event of interest, a cure rate model can be an appropriate and useful method to estimate cure fraction and model the rate of cured people directly (1). Cure models are categorized in two different major groups: The mixture and non-mixture cure fraction models. Non-mixture cure model or bounded cumulative hazard model are utilized to model both group, cure fraction, and survival parts of the model by specific approaches (5).

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3 Revision 2

1 comment · 6 May 2020

Associate Editor

MINOR REVISION 6 May 2020

Many thanks for submitting your manuscript to IJCM. Your manuscript has been reviewed by our specialist, and you can find their comment below:
1. What are the reference numbers for the first paragraph of the introduction?

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

We added 3 references in paragraph I of introduction.
ORCID number of the first and corresponding author was added too.

Hamid Reza Khalkhali
http://orcid.org/0000-0003-2837-0735

Rasool Gharaaghaji
http://orcid.org/0000-0002-8066-707X
Unfortunately we could not enter in the system and maybe the system was not working right.
So many thanks

4 Revision 3

3 comments · 6 Jul 2020 – 26 Jul 2020

Referee 1 Reviewer

MINOR REVISION 6 Jul 2020

1- Phrases such as "didn't", "don't", and "can't" have been frequently used in the text. This paper is a formal academic research paper, and according to writing standards, contractions are not recommended.

2- The opening paragraph of Section 4 indicates that the present study is a "prospective study", whereas it seems to be a retrospective one.

3- A relevant reference or references should be given next to the AIC equation in section 3.

4- An important part of the proposed survival model, which allows one to specify the influence of given risk factors, is an embedded regression model. Then, the maximum likelihood estimation method is used for parameter estimation. The regression equation should be shown mathematically, and the likelihood function should be presented. For example, it is not clear which covariates are used in the ratio part of the model and which ones are used for the survival function.

5- The same parameters have been used in the equations, which causes a great deal of confusion. For example, in section 3, "p" plays the role of a distribution parameter, and at the same time it is used to denote the ratio part of the MCM. In addition, the mathematical relationships (inside the paragraph) below equation (19) have been displaced and are not clear.

6- "Age of Marriage" has been declared to be one of the significant factors, and, as a matter of fact, research results imply that marriage before age 20 can mitigate the risk of failure in a significant way. It is a continuous variable that has been discretized using a predefined threshold (20 years), which is also emphasized in the interpretation of the results. I wonder how influential this threshold can be and to what extent a different threshold can change the result of estimation and consequently the interpretation of the results. Do you have access to the initial values of the variable before conversion into a binary variable?

7- In table 2, the ratio is of interest and should be restricted to the unit interval. Why has the upper limit exceeded one?

8- Conclusions should be presented in more detail. The present paragraph has mentioned only the purpose of the study. It should provide clear answers to the research questions in a concise manner. Besides, avenues for further studies or research are provided here.

9- As the final comment, it should be noted that "Conflict of Interests" includes not only the interests of the authors themselves but also those of any other beneficiaries, including persons or organizations. Therefore, for example, if the interests of patients or an organization are at risk in some way or are related to the revealed results of the paper, this should be clearly stated in the "Conflict of Interests" section.

Associate Editor

MINOR REVISION 25 Jul 2020

Needs to be revised.

Editor-in-Chief MINOR REVISION 26 Jul 2020

Dear authors,
Please revise your manuscript according to the reviewer's comments.

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Response to dear reviewer,

Reviewers' Comments:

Reviewer 1:

1- Phrases such as "didn't", "don't", "can't" have been frequently used in the text. This paper is a formal academic research one, and according to writing standards, contractions are not recommended.

Response: You are right, we did all requested changes and highlighted in yellow color.

2- Section 4, in the beginning paragraph, indicates that the present study is a "prospective study", whereas it seems to be a retrospective one.

Response: You are right, we analyzed prospectively but the collection of the data was done respectively. It was changed to "respective".

3- Relevant reference or references should be given next to the AIC equation in section 3.

Response: The following reference was entered in the text and references list.

Bozdogan H. Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. Psychometrika. 1987 Sep 1;52(3):345-70.

4- An important part of the proposed survival model which allows specifying the influence of given risk factors is an embedded regression model. Then, maximum likelihood estimation method is used for parameter estimation. Regression equation should be shown mathematically, and the likelihood function should be presented. For example, it is not clear which covariates are used in the ratio part of the model and which ones are used for the survival function.

Response: Dear reviewer, actually the journal is a clinical journal and we tried to not use more statistics and equations. We tried to write in ease to be readership by other researchers.

5- The same parameters have been used in the equations which causes a great deal of confusion. For example, in section 3, "p" plays the role of distribution parameter, and at the same time it is used to denote the ratio part of the MCM. In addition, mathematical relationships (inside the paragraph) below equation (19) have been displaced and are not clear.

Response: We changed in detail. Additionally we checked the site https://medium.com/analytics-vidhya/probabilistic-model-selection-with-aic-bic-in-python-f8471d6add32 to complete your request.

$$AIC = -2 * \log(likelihood) + 2 * (p + k)$$

Where P is the number of parameters in the model and k is 2 in AIC and log (sample size) in Bayesian information criterion (BIC). Indeed, the k coefficient for log-normal, log-logistic, and Weibull models is 2.

6- "Age of Marriage" has been declared as one of significant factors and as a matter of fact, research results imply that marriage under 20 can mitigate the risk of failure in a significant way. It is a continuous variable which has been discretized using a predefined threshold (20 years) which is also emphasized in the interpretation of the results. I wonder how influential this threshold can be and to what extent a different threshold can change the result of estimation and consequently the interpretation of the results. Do you have access to initial values of the variable before conversion into a binary variable?

Response: The threshold of 20 years was selected based on the culture, clinician consultation and literature review.

7- In table 2, the ratio is of interest and should be limited in the unit interval. Why has the upper limit exceeded one?

Response: It was a typo error. The limit is 0.29 -0.51 with p value of 0.05.

	Safe patients' ratio	Fiducial interval		P value
		Lower limit	Upper limit	
Cox cure model	**0.40**	**0.29**	**0.51**	**0.05**

8- Conclusions should be presented in more detail. The present paragraph has mentioned only the purpose of the study, It should provide clear answers to the research questions in a concise manner. Besides, avenues for further studies or research are provided here.

Response: Dear reviewer, our purpose was to compare two cure models and it was written.

9- As the final comment, it should be noted that "Conflict of Interests" not only includes the interests of authors themselves but also of any other beneficiaries including persons or organizations. Therefore, for example, if interests of

patients or an organization are kind of at risk or related to the revealed results of the paper this should be clearly stated in the "Conflict of Interests" section.

Response: it is written in detail as following:

There are no conflicts of interest between authors regarding affiliation with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

5 Revision 4

2 comments · 3 Oct 2020 – 3 Oct 2020

Associate Editor

ACCEPT 3 Oct 2020

All the comments of the reviewer are acceptable.

Editor-in-Chief

MINOR REVISION 3 Oct 2020

Dear author,
Please revise your manuscript according to the reviewer's comments.

6

Revision 5

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor in chief

First of all, we want to convey our thanks to the respected Reviewers and Editors for the valuable comments which made our article more improved in every aspect after revision. We have modified the manuscript accordingly. The modifications and the added texts to the manuscript are highlighted in YELLOW or using track changes in the word file. The detailed corrections are listed below:

Reviewers' Comments:

- In line 132, summation symbol is missed in two consecutive positions in the same line which has made the relationships meaningless.

Answer: It is edited in the text.

$S(t)=\sum_{i=1}^{k} p_i S_i(t) . \sum_{i=1}^{k} p_i=1$

- In line 146, the power symbol should be omitted.

Answer: It is edited in the text.

$S^*(\infty) = 1-p$

- In the paragraph between lines 127-134, index I should be written as a subscript.

Answer: It is edited in the text.

Similarly, cure models can be divided into two types: mixture and non-mixture cure models. In the mixture models, the population is assumed to be composed of k subgroups and distribution of survival time of members in each subgroup is considered to be different from that of the others. So, let p_i and $S_i(t)$ be the ratio and the survival function of members of the subgroup i respectively. Then, based on the mixture models, the survival function of the entire population is $S(t)=$

$\sum_{i=1}^{k} p_i S_i(t) . \sum_{i=1}^{k} p_i = 1$. In these models, the parameters are estimated using the maximum likelihood method. In the likelihood function formula, p_i itself is a parameter of the model and must be calculated.

- In line 111, multiplication symbol is a programming symbol and it could either be omitted or replaced with its mathematical counterpart.

Answer: It is edited in the text.

$$AIC = -2 \times \log(likelihood) + 2 \times (k)$$

Where k is the number of parameters in the model which is a constant coefficient depending on type of the model used.

- In my fifth comment I had requested clarification about parameter “p” which serves different purposes in different parts of the section 3, however, the answer deals with the AIC relationship and does not address the requested modification properly.

The formula and the definition of parameter is edited in the text:

$$AIC = -2 \times \log(likelihood) + 2 \times (k)$$

Where k is the number of parameters in the model which is a constant coefficient depending on type of the model used.

- In the sixth comment, the sensitivity of the results to the threshold and the accessibility of the original observations have been questioned, whereas, the answer does not provide a direct explanation to the subject of interest in the comment.

We added the variable of age of marriage as a continuous variable in both univariate and multivariable model of our study, the effect of this variable on both the long-term and the short term survival time of patients with cervix cancer was the same as what we obtained by using this variable as a categorical variable in the model. We could report both results in the appendix and discussion if you think it is necessary.

The results of the analysis are provided blow:

Risk Factors	Weibull model				Log-logistic model				Log-normal model			
	cure chance	Fiducial interval		p-value	cure chance	Fiducial interval		p-value	cure chance	Fiducial interval		p-value
		upper limit	lower limit			upper limit	lower limit			upper limit	lower limit	
Age of marriage	0.12	0.63	0.06	0.044	0.16	0.47	0.10	0.032	0.28	0.83	0.13	0.025

Table 3. The univariate analysis of the cure parametric models

Table 4. Multiple analysis of the cure parametric models for susceptible subjects(cure)

Risk Factors		Weibull model				Log-logistic model				Log-normal model			
		cure chance	Fiducial interval		p-value	cure chance	Fiducial interval		p-value	cure chance	Fiducial interval		p-value
			upper limit	lower limit			upper limit	lower limit			upper limit	lower limit	
Recurrence of the disease	No	base group				base group				base group			
	Yes	3.29	5.14	1.43	0.001	3.38	5.87	0.90	0.008	7.19	37.16	2.23	0.039
Age of marriage		0.12	0.34	0.10	0.013	0.16	0.66	0.02	0.013	0.28	0.65	0.09	0.047

Table 5. Multiple analysis of the cure parametric models for susceptible subjects(survival)

Risk Factors		Weibull model				Log-logistic model				Log-normal model			
		Relative Risk	Fiducial interval		p-value	Relative Risk	Fiducial interval		p-value	Relative Risk	Fiducial interval		p-value
			upper limit	lower limit			upper limit	lower limit			upper limit	lower limit	
Recurrence of the disease	No	base group				base group				base group			
	Yes	2.49	6.77	1.18	0.023	2.89	68.20	1.85	0.046	0.92	1.75	0.10	0.027

Age of marriage	0.08	0.20	-0.31	0.674	0.10	2.24	-0.45	0.564	2.07	4.25	-0.09	0.073

- And finally, authors have provided a reference for AIC relationship [Bozdogan H. Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. Psychometrika. 1987 Sep 1;52(3):345-70], however, it does not include the specific relationship used in line 111.

We added some related references in this part:

Akaike, H. (1973). Information theory and an extension of the maximum likelihood principle. Second International Symposium on Information Theory, pp. 267-281.

Bishop, C. (1995). Neural Networks for Pattern Recognition. Clarendon Press, Oxford.

Cover, T. & Thomas, J. (1991). Elements of Information Theory. Wiley, New York.

Breiman, L., Friedman, J., Olshen, R. & Stone, C. (1984). Classication and Regression Trees. Wadsworth.

Ripley, B. D. (1996). Pattern Recognition and Neural Networks. Cambridge University Press.

- The last parenthesis of AIC equation which includes parameter k (supposed to be 2) which is not used in the given reference. Hence, the equation might need a revision.

The whole formula and the definition of k is edited in the text.

The AIC value for the models used in this research was calculated using the following formula:

$$AIC = -2 \times \log(likelihood) + 2 \times (k)$$

Where n is the number of parameters in the model depending on type of the model used. The lower the AIC, the better will be the performance of the model.

6 Revision 5

1 comment · 5 Dec 2020

Referee 1 Reviewer

ACCEPT 5 Dec 2020

While appreciating the efforts of the authors, I believe that the main problems of the paper (ID: 93966) have been resolved and it can be accepted.