Review Article

Gastric Cancer Survival Analysis: Applying the Bayesian Mixture Cure Rate Frailty Models

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ABSTRACT

Background: Bayesian mixture cure rate frailty model is a model used in survival analysis by controlling frailty when the fraction of cured individuals exists. The present study was performed as the first systematic review in survival analysis with cure fraction. The aim of this systematic review was to study and evaluate the related studies on Bayesian mixture cure rate frailty model. Also, this model was used to demonstrate its importance and applicability in determining the variables affecting the survival of patients with gastric cancer.

Methods: This systematic review was done based on the PRISMA guideline by considering related searching keywords in PubMed, Scopus, Science Direct, Web of Science, and Google Scholar. Also, Bayesian mixture cure rate frailty model was used to analyze gastric cancer data.

Results: In the beginning, 882 studies related to survival analysis of cure rate model were found. Finally, by reading the full-text, only 4 related studies were found based on the inclusion and exclusion criteria. In these studies, semi-parametric models and parametric model with Weibull distribution were used for time-to-event data. Also, based on the results of the model, significant and affective variables on the survival of patients with gastric cancer were found.

Conclusion: According to the results of this study, in the cure model, choice of proper distribution for the frailty variable and baseline distribution can influence the results. It was also found that place of residence, chemotherapy, morphology, and metastasis are effective variables on survival of patients with gastric cancer.

Keywords: Gastric cancer, Survival, Systematic review, Mixture cure rate model, Frailty model, Bayesian inference

Introduction

Generally, if a study continues sufficiently, it is expected that the event of interest happens to all people present in the study. However, this assumption is not always true. In such studies, it is said that individuals are cured or immune in relation to event of interest (1,2). If a considerable number of patients are cured and the status of being cured is important, the population under study will be a mixture of susceptible and non-susceptible individuals who will face the event. In such cases, the use of proportional hazard cox model is not appropriate, as this model assumes that all individuals have the same risk of experiencing an event and that all individuals will finally experience the event over a long period of time (3,4). In other words, in survival analysis studies, curing means that the event of interest will not occur to some individuals or will occur over a long period of time, or it can be stated that some individuals present in the study are at the same risk of the event as the reference population under study (1,5). Cure models consider individuals who are cured or have long-term survival time in analysis. Also, this model takes the heterogeneity of individuals into consideration which causes some to have longer survival rate and some shorter survival rate (4).

Due to recent scientific improvements in the field of cancer treatment, a significant number of patients are cured. In cure models, it is supposed that large numbers of individuals are cured and the corresponding hazard is zero for them (6). On the other hand, due to high mortality rate of cancer in its final stages, if this disease is diagnosed in the first stages, a great percentage of individuals will have long-term survival time or even will be recovered. In other words, in some cases, a large number of cancer patients can have long-term survival time. Thus, considering the scientific improvements in the field of cancer treatment and long-term survival time of some patients, cure models are beneficial tools for describing and analyzing cancer survival rate (7).

The most common and practical cure model is mixture cure rate model. In this study, the participants were divided into 2 groups: One group of cured individuals and one uncured for whom the event of interest has happened (2,8). One of the important benefits of mixture cure rate model is that it allows the researcher analyze the effect of different variables on cured and uncured individuals separately (7). Survival function in the mixture cure rate model is given by the following equation 1:

$$S(t) = p + (1-p)S_0(t) \quad (1)$$

where, p is cure fraction and $S_0(t)$ is the baseline survival function in individuals for whom event of interest has happened (9-11). Hazard function in the mixture cure model is calculated by the following formula (Eq. 2):

$$h(t) = \frac{(1-p)f_0(t)}{p+(1-p)S_0(t)} \quad (2)$$

Hazard function is considered for all the individuals under study (3).

Sometimes, the heterogeneity existing among observations can affects results. The heterogeneity is caused by omitting or neglecting a collection of significant and effective variables on events or by correlations among observations (12). This heterogeneity causes frailty to be different for individuals. It means that some individuals experience events more rapidly than others. If frailty varies excessively among individuals, it will affect results and cause wrong estimation of coefficients. For solving this problem and considering both correlation and heterogeneity among observations, frailty models are used (13-15). Moreover, for considering the frailty variable in a model, survival and hazard functions in survival analysis by conditioning on the frailty variable are given as (Eq. 3,4):

$$S(t|z) = S(t)^z \quad (3)$$
$$h(t|z) = zh(t) \quad (4)$$

where, z is the frailty variable, $S(t)$ is the survival function, and $h(t)$ is the hazard function. The frailty model with gamma distribution is the most common model; however, when there are types of cure fraction model in survival data, the use of continuous distribution like gamma distribution may not be appropriate for the frailty

variable (16). The reason is that individuals with long-term survival time have zero frailty, but continuous distribution for frailty cannot have zero risk (13,17).

When the goal of a study is to determine the best fitted model in two states of classical inference and Bayesian inference, it is necessary to mention the logic of Bayesian methods. Bayesian inference methods for survival data with cure fraction were first introduced by de Castro *et al*. (18), Chen *et al*. (11), Chen & Ibrahim (8), Kim *et al*. (6), and Seltman *et al*. (19).

In Bayesian analysis, posterior distribution is highly important and results are achieved from this distribution. Posterior distribution is applied to calculate the parameters of a model by combining prior distribution and likelihood function using the Bayes theorem, which is given by equation 5:

$$p(\theta|X,\alpha) = \frac{p(\theta,X,\alpha)}{P(X,\alpha)} = \frac{p(X|\theta,\alpha).p(\theta,\alpha)}{p(X|\alpha).p(\alpha)} = \frac{p(X|\theta,\alpha)}{p(X|\alpha)}.p(\theta|\alpha) \propto L(X|\theta,\alpha).p(\theta|\alpha) \quad (5)$$

where, X is the covariate of interest, θ is the parameter, α is the hyper-parameter, $p(\theta|\alpha)$ is the prior distribution, $L(X|\theta,\alpha)$ is the likelihood function, and $p(\theta|X,\alpha)$ is the posterior distribution. Although determining posterior distribution for parameters of a model is somehow complicated, with the use of simulation techniques such as the Markov Chain Monte Carlo (MCMC) algorithm, we can easily produce samples of posterior distribution and overcome this complication (20,21). To this end, practical statistical software such as OpenBUGS and R can be used (1,22). The data distribution and prior distribution of parameters should be determined here in order to be able to use Bayesian inference with the use of the above-mentioned software. Further, for comparing the Bayesian model with the classical model, statistical indices such as deviance information criterion (DIC), expected Bayesian information criterion (EBIC), and expected Akaike information criterion (EAIC) are used (3,14,18).

One of the practical techniques to properly express advantages and disadvantages of a model or a method is the use of a systematic review. With the use of a systematic review, all studies related to issues of interest can be gathered and used for describing and analyzing results (23,24). Therefore, the present study was conducted as the first systematic review in survival analysis with cure fraction, in which frailty is induced. Generally, summarizing research results, identifying the process of research, and achieving a proper guideline for researches of interest about Bayesian mixture cure rate models induced by frailty in survival

analysis were among the purposes of this systematic review. Moreover, it was aimed to express the importance of using Bayesian mixture cure rate models induced by frailty in survival analysis with cure fraction. The systematic review also aimed to determine methods of using Bayesian mixture cure rate models induced by frailty on different data as well as methods of analyzing the correctness of obtained results. Among other goals of the systematic review was expressing advantages and disadvantages of using Bayesian mixture cure rate models induced by frailty. Also, Bayesian mixture cure rate frailty model was used to demonstrate its importance and applicability in order to determine the variables affecting the survival of patients with gastric cancer.

This study was suggested to provide researchers with information about Bayesian mixture cure rate models induced by frailty and help those who intend to do survival analysis with cure fraction research. Moreover, to solve the problems in these studies, it was decided to perform another complementary research in order to take a step forward to improve the proposed models.

Materials and Methods
Literature search strategy

In the present systematic review, articles of interest were selected based on the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guideline (25). In this study, the article search was done in Web of Science, Science Direct, Scopus, and PubMed

databases only in English language and without any limitation of year of publication. The searching strategy was first to search for all articles related to cure models. As none of the keywords of interest existed in medical subject headings (MeSH), it was decided to search for a large desired number of articles in order to not miss any relevant and important article. Accordingly, 979 articles were found with the use of seven related cure model keywords consisting of "cure model", or "cure rate model" or "cure fraction" or "cure rate fraction" or "surviving fraction model" or "survival models with a surviving fraction" or "long-term survival model", and also, with the use of the following strategy. Moreover, in addition to the above-mentioned databases, Google Scholar was used and the manual search of references of relevant articles was performed.

Study selection

All the selected articles were transferred to the Mendeley software and duplicated articles were excluded, resulting in a final set of 882 articles. The remaining articles were those, in which related words of cure models existed. The

inclusion criterion was articles, in which cure models were used for survival analysis.

Inclusion and exclusion criteria

The inclusion criterion in the present systematic review was mixture cure rate models. Thus, in this systematic review, articles with mixture cure rate models as their analysis models were selected. The present study also had several exclusion criteria, including articles with competing risks modeling or multivariate survival data, articles whose data were clustered as survival data, and articles in which joint models were used for longitudinal and survival data.

Data extraction

In the present systematic review, data extraction was performed twice in order to avoid any error. From the articles in the systematic review, baseline distribution, frailty distribution, status of stimulated study, status of comparing mixture cure rate models with non-mixture ones, and methods used in Bayesian reference were extracted.
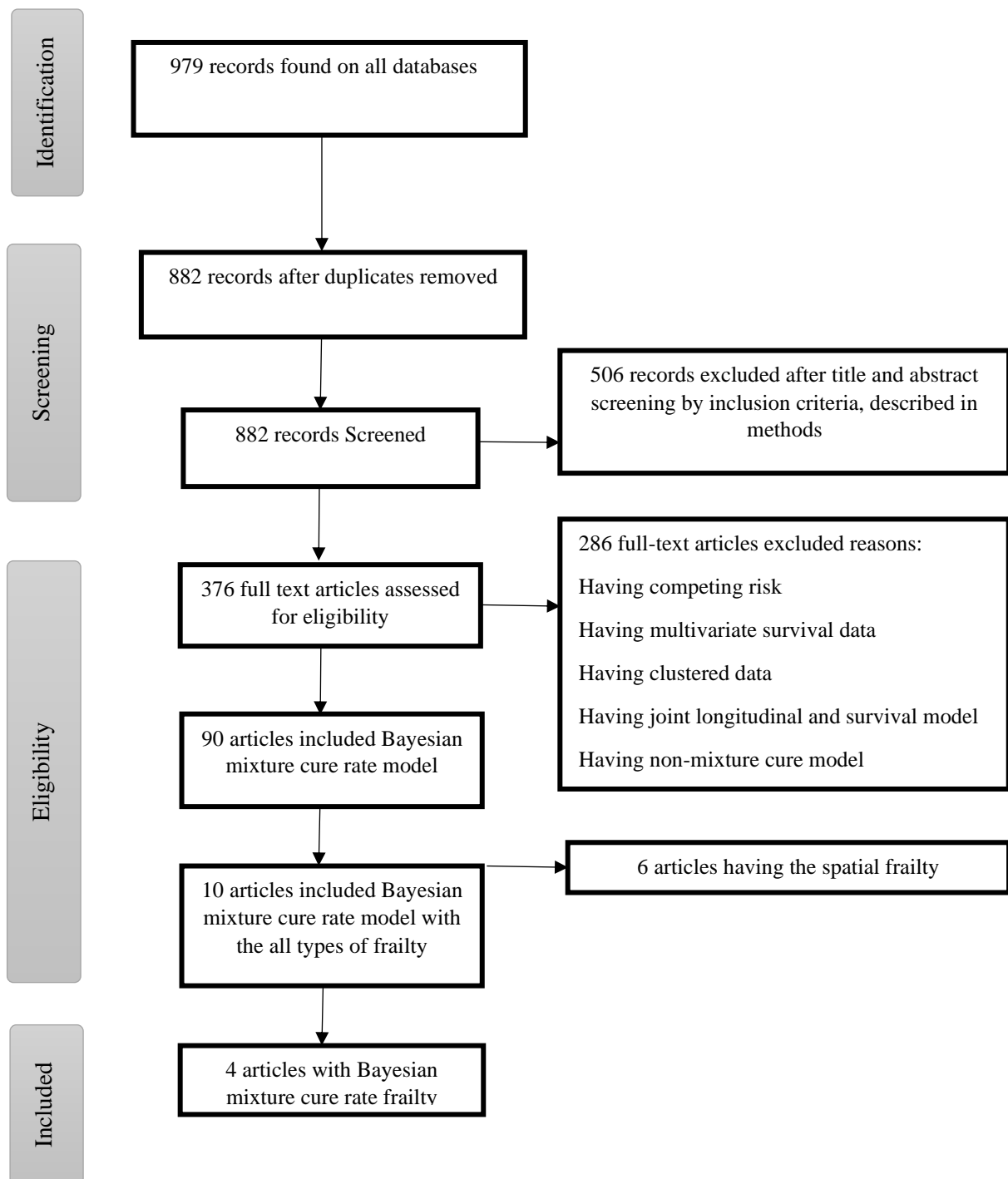
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Identification

979 records found on all databases


Screening

882 records after duplicates removed


882 records Screened                    506 records excluded after title and abstract
                                        screening by inclusion criteria, described in
                                        methods


376 full text articles assessed         286 full-text articles excluded reasons:
for eligibility
                                        Having competing risk

                                        Having multivariate survival data

                                        Having clustered data

Eligibility                             Having joint longitudinal and survival model

90 articles included Bayesian           Having non-mixture cure model
mixture cure rate model


10 articles included Bayesian           6 articles having the spatial frailty
mixture cure rate model with
the all types of frailty


Included

4 articles with Bayesian
mixture cure rate frailty
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Figure 1. PRISMA flow diagram.

Bayesian mixture cure rate frailty model was used to determine factors affecting survival of patients with gastric cancer. For this purpose, the generalized modified Weibull distribution for time-to-event and the hyper-Poisson distribution for the frailty variable were used. In the Bayesian inference, an appropriate distribution was considered as the prior distribution for each of the parameters in the model. Based on the prior distribution and the likelihood function, the posterior distribution was calculated and a dataset of 250,000 samples was generated using the Metropolis Hasting algorithm for each parameter. Among them, the first 50,000

samples were considered as burn-in period and excluded from the model to minimize the effect of initial values. Also, the value of thinning was adjusted to 100 to minimize the effect of correlation between the generated values. Finally, 100 replications were performed for each configuration and the mean values, standard deviation, and credible interval of 95% were estimated for each of the parameters and regression coefficients. Therefore, the data were analyzed using Bayesian mixture cure rate model with taking into account controlling frailty effect by programming and executing the required instructions in R 3.5.1 statistical software.

Results

In the present study, based on the determined inclusion and exclusion criteria in the method section, from 882 articles, 376 were related to cure rate models. In the next step, after studying the topics and abstracts of the selected articles, 90 articles were extracted, in which in addition to mixture cure rate models, Bayesian methods were used for result inference. Since frailty was also important to us and was discussed very briefly in the abstract, the selected articles were studied in full. By doing so, of all the remaining articles, 10 related articles were found. Finally, from among them, articles used under the condition of spatial frailty were excluded. Finally, four related articles remained, which in addition to being related to mixture cure rate models, used frailty with the use of Bayesian inference. The obtained results are all presented in Figure 1.

In a study entitled "a Bayesian cure rate model with dispersion induced by discrete frailty" by Cancho *et al.* in Brazil (2018), the results of several models were compared with each other in a way that Weibull distribution was used for baseline distribution. By comparing zero-inflated geometric (ZIG), zero-inflated Poisson (ZIP) and geometric models based on the values of AIC, BIC, and DIC, it was specified that the best suggested model for Melanoma data was the ZIG model. In this study, frailty distribution was given more attention and importance than baseline distribution. Bayesian inference with the use of the MCMC algorithm was used in this study. Moreover, a simulation study was conducted to evaluate the suggested model and the calculation algorithm. Overall, it was concluded that ZIG and ZIP distributions

function better than Poisson distribution for frailty parameter (26).

In a study entitled "a semi-parametric cure model for interval-censored data" by Lam *et al.* in America (2012), a semi-parametric model was used. In their study, two collections of data about melanoma and breast cancer were used. Here, Poisson distribution was used for the frailty parameter. Generally, they attempted to evaluate the effect of the existing variables on cure fraction and survival function. Based on the comparison of semi-parametric cure models with those uncured, it was revealed that if an uncured model was mistakenly used among the cured individuals, the significance of the results would be affected. They only used Bayesian inference for melanoma, which was right-censored. It was also revealed that frailty was better to be controlled in the model in order to obtain precise results. Moreover, by the use of a simulation study, it was revealed that the suggested model was appropriate. Finally, the suggested model was compared with the promotion time model. They concluded that the novelty of the suggested model was separate evaluation of the effect of variables on both short- and long-term survival time (27).

In another study entitled "Bayesian cure rate models induced by frailty in survival analysis" by de Souza *et al.* (2017), Weibull distribution for baseline distribution and hyper-Poisson distribution for frailty were used. Moreover, in this study, like other studies, it was revealed that the mean measure of parameters resulting from simulation was really near to the value of parameters declared in the study. Thus, they concluded that the used model was appropriate. It was also shown that for mixture cure rate models, by increasing sample size, samples verifying the model of interest increased; however, sample size decreased for non-mixture cure rate models. They also concluded that the hyper-Poisson cure model with one variable was better than the promotion time model. The interesting result is that in their study, the promotion time model functioned better than the hyper-Poisson cure model in the presence of all variables. The reason was that with the use of uniform distribution for a dispersion parameter, much information was lost. They also used melanoma data in their study. Finally, the basic result achieved from their study was that hyper-Poisson distribution for frailty was precise and appropriate when there was cure fraction (13).

In a study entitled "Bayesian superposition of pure-birth destructive cure processes for tumor latency" by Rodrigues *et al.* (2018), they used melanoma data as in other studies. Moreover, they used a semi-parametric cure model by considering Poisson distribution for frailty and simultaneously analyzed the effect of several variables on long- and short-term survival. Another result in their study is that the Hamilton Monte Carlo method was more efficient in Bayesian inference than Metropolis-Hastings and Gibbs Sampling algorithms (28). All data extracted from the articles studied in the present study are presented in Table 1.

Table 1. Data extraction

ID	Title	Authors (year)	Time to Event Distribution	Frailty Distributions	Simulation Study	Non-mixture Cure Model	Method for Bayesian Inferences (MCMC)
1	A Bayesian cure rate model with dispersion induced by discrete frailty (26)	Cancho *et al.* (2018) (26)	Weibull	Poisson and Geometric	Yes	No	Gibbs samplings and Metropolis-Hasting
2	A semi-parametric cure model for interval censored data (27)	Lam *et al.* (2013) (27)	Semi-parametric	Poisson	Yes	Yes	Gibbs samplings and Metropolis-Hasting
3	Bayesian cure rate models induced by frailty in survival analysis (13)	de Souza *et al.* (2017) (13)	Weibull	Hyper Poisson	Yes	Yes	Gibbs samplings and Metropolis-Hasting
4	Bayesian superposition of pure-birth destructive cure processes for tumor latency (28)	Rodrigues *et al.* (2012) (28)	Semi-parametric	Poisson	Yes	No	Hamilton Monte Carlo

Due to the existence of cured data in the studied data, Bayesian mixture cure rate frailty model was used to analyze the data. The model results are shown in Table 2.

Table 2. Estimates of parameter in Bayesian mixture cure rate frailty model for short-term survivor

Parameters	Mean	Std. Dev.	95% Credible Interval
α	0.21	0.06	(0.11, 0.37)
β	1.62	0.28	(1.17, 2.27)
γ	0.35	0.05	(0.26, 0.48)
λ	0.02	0.003	(0.01, 0.03)
η	2	1.41	(2.00, 6.00)
Intercept	1.80	1.49	(-1.30, 4.54)
Place of residence			
Rural	-0.26	0.16	(-0.61, -0.03)
Urban	0		
Chemotherapy			
Yes	-0.30	0.15	(-0.63, -0.03)
No	0		
Morphology			
Neoplasm	-0.83	0.23	(-1.25, -0.42)
Adenocarcinoma	0		
Metastasis			
Yes	0.38	0.22	(0.01, 0.78)
No	0		

As shown in Table 2, place of residence, chemotherapy, morphology, and metastasis are variables that influence patient survival. According to the results of this study, urban patients had a higher risk of mortality occurrence caused by gastric cancer compared to rural patients. Patients with metastasis had a higher risk of mortality occurrence caused by gastric cancer compared to those without metastasis. On the other hand, patients who did not receive chemotherapy had a higher risk of mortality occurrence caused by gastric cancer compared to those who received chemotherapy. In terms of morphology variable, it can be also argued that patients with adenocarcinoma status had a higher risk of mortality occurrence compared to those with neoplasm status.

Discussion

In the present study, we finally reached four articles, in which Bayesian mixture cure rate models induced by frailty were used. In these studies, for baseline distribution, the model with Weibull distribution or the semi-parametric model was used. The reason was that these two models were more efficient for cured individuals because of the nature of data (29). Moreover, in most of the articles, discrete distributions, especially Poisson distribution, were used for frailty distribution. The reason might be that there was cure fraction among individuals under study and for these individuals, frailty was zero and continuous distribution could not be used, as probability in one point is zero in continuous distribution (17).

In all these studies, melanoma data were used, as the death probability of patients with melanoma is low and its growth will be prevented very fast if diagnosed early (30). Moreover, all factors cannot be identified or measured for diagnosing this cancer. Thus, for these data, the use of a cure model with frailty is appropriate. But in the present study, gastric cancer data were used to demonstrate the capabilities of this model in analyzing other data.

Since in some related studies about cured individuals, the distribution of the number of risk factors is important as it leads to different frailty rates in individuals, usually Poisson distribution is used for this variable (13). As it was mentioned before, in one study, in addition to Poisson distribution, geometric distribution was used. The result indicated that geometric distribution of data of interest acted better than Poisson distribution. The reason might be that in

Poisson distribution, under- and over-dispersion are not considered, which may be due to the nature of data causing either of them to occur. In conclusion, it can be stated that one of the advantages of a model with geometric distribution over a model with Poisson distribution is that the mean and variance of data of interest are highly different. It should be noted that for these two distributions, if many zeros exist in data, zero-inflated methods should be used to analyze the data. It is suggested to use hyper-Poisson distribution instead of using these distributions and considering the status of zero-inflated to analyze data because it does not have any problems with many zeros in the data collection procedure. In this distribution, in addition to the parameter of Poisson distribution, there is another parameter called dispersion, which does not have any problems with under- or over-dispersion (31). In Bayesian discussion, depending on which distribution is used for parameters of interest, there might be great differences among models. Usually beta prior distribution is used for the parameter of geometric distribution whereas gamma prior distribution is used for the parameter of Poisson distribution (32).

About the incorrectness of the results during cure fraction in survival analysis, a model which does not consider this curing percentage in analysis is used. It should be noted that the current survival model works with this assumption that all individuals have the same risk of experiencing an event of interest, and finally, they all will experience it. Cured individuals will never experience the event of interest. This is why being cured in such a cure model is taken into consideration to lead to more precise results. Based on the results of these articles, it is better to control frailty in order to obtain more precise results. As it is obvious, sometimes there might be heterogeneity among observations, which might prevent measuring some important and effective factors as well as their effect in the model.

About mixture and non-mixture cure models, it can be mentioned that each of these models has its own application and it is not easily understood which applications are better than others. About non-mixture cure models, since these models are considered as the Cox model, their semi-parametric models are not defined separately from the Cox model, and thus, only parametric models are useful for these models (7). As a result, in most cases, parametric models

are used for comparing the results of mixture cure models and non-mixture cure models.

About methods used in Bayesian inference, it should be stated that although some methods like Gibbs sampling and Metropolis-Hastings are frequently used, some other methods such as Hamilton Monte Carlo might better fit data. Therefore, it is worth mentioning that based on the nature of data as well as the model condition and distributions used, a method may deliver more precise results, which has been less used in previous studies. Accordingly, it is recommended to compare several methods in order to use the most appropriate method so that the most precise results can be obtained.

Generally, for improving the results of a study, in which Bayesian mixture cure rate models with frailty are used for the analysis purpose, it is suggested to use hyper-Poisson distribution instead of Poisson distribution for the frailty variable in the first step, and also, use generalized modified Weibull distribution instead of Weibull distribution for baseline distribution. As mentioned before, the advantage of hyper-Poisson distribution is that we do not need to worry about under- and over-dispersion. The generalized modified Weibull distribution is a complementary of Weibull distribution and is well-used for any kind of data based on its parameters and shape. Additionally, this distribution has a parameter called the accelerating factor, which measures the survival fragility of individuals over time. The study that uses both of these distributions simultaneously is the first study.

Variables of place of residence, chemotherapy, morphology, and metastasis were effective variables on survival of patient. The risk of mortality occurrence caused by gastric cancer is lower among rural residents than in urban residents. It may be due to the conditions in the village, such as healthy foods, less air pollution, and less stress among rural people than urban residents. On the other hand, when the patient has metastasis, the disease is in critical condition. Therefore, it can be expected that persons with metastasis are more likely to experience the event of mortality caused by gastric cancer compared to those without metastasis (33). The results of the present study also showed that the risk of mortality was higher for persons with metastasis compared to those without metastasis. In the case of chemotherapy, it is expected that those who receive chemotherapy are less likely to experience the

event than others because of the high importance and the improvement in patients receiving this treatment (34-37). The status of adenocarcinoma for gastric cancer is also worse due to the presence of the cancer cells in the inner layers including the glands compared to the status of neoplasm where some cells are not malignant (33,38). Therefore, patients with adenocarcinoma experience a higher rate of the event of interest.

Limitations

The present systematic review had also some limitations. Since the keywords of interest did not exist in MeSH, we had to search for a large number of articles in order to not miss any study, which was greatly time-consuming. The other limitation was that only English articles were evaluated, and also, studies published after March 2019 were not included. Moreover, in this systematic review, the databases mostly used were those whose journals were mostly related to medical sciences.

Conclusion

The general result achieved in this study is that in cure models induced by frailty, Poisson distribution for the frailty variable and Weibull distribution for baseline distribution are the most common distributions for these two parameters, but are not always the most complete ones. For more important and precise distributions, hyper-Poisson for the frailty variable and the generalized modified Weibull distribution for baseline distribution can be mentioned. In survival analysis with cure fraction, when all effective factors are not measurable, the model considering frailty should be used. By doing so, we can be sure about the precise effect of a specific variable on the survival of patients and individual's frailty is controlled. The problem that may arise here is that by choosing the wrong distribution, significantly the results and estimated coefficients are affected, so that the results may be completely different. However, it should be mentioned that the chosen distribution for frailty when there is cure fraction should definitely be discrete distribution. Concerning the variables affecting the survival of patients with gastric cancer, it is concluded that place of residence, chemotherapy, morphology, and metastasis are important factors affecting the survival of patients. Therefore, in order to improve gastric cancer patients, it is

recommended to pay more attention to these variables.

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