Original Article

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TANAFFOS

Application of Mixture Cure with the Doubly Censoring Model in Estimation of Initiation Age and Prevalence of Water-Pipe Smoking in Iran: a New Approach in Population-Based Studies

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Background: The initiation age and prevalence of smoking water-pipe are two important parameters for establishing preventive policies. Thus, the present study was conducted to introduce a new approach for estimating and evaluating the effect of demographic variables on the initiation age and prevalence of smoking water-pipe.
Materials and Methods: The STEPwise approach for non-communicable disease risk factors surveillance (STEPS) 2011 data were used and daily smokers and non-smokers with the age range of 16 to 70 years were included in the study. A survival mixture cure rate model with doubly censoring was used.
Results: Totally, 9764 individuals were enrolled in the study. No significant association was observed between the initiation age and gender (HR=1.07, 95% CI: 0.76, 1.58), whereas there was a significant difference between initiation age and area of residence (HR=0.62, 95% CI: 0.44, 0.88). The mean age of starting smoking was 25.82 years (95% CI: 24.13, 27.63). The odds of smoking in men were higher than in women (OR=2.34, 95% CI: 1.79, 3.7). The prevalence of smoking had a significant association with socioeconomic status (OR=0.84, 95% CI: 0.72, 0.97), but no association with the level of education (OR=1.06, 95% CI: 0.97, 1.15) and place of residence (OR=1.2, 95% CI: 0.93, 1.57) was found. The estimated prevalence of smoking water-pipe in total, men, and women was 4.8% (95% CI: 4.19%, 5.51%), 7.77% (95% CI: 6.76%, 8.86%), and 3.47% (95% CI: 2.8%, 4.25%).
Conclusion: A new statistical methodology was applied to estimate and evaluate the effect of demographic variables on the initiation age and prevalence of water-pipe smoking.

Key words: Smoking Water Pipe; Initiation Age; Prevalence; Parametric Survival Mixture Cure Model with Doubly Censoring; STEPs

INTRODUCTION

Nowadays, non-communicable diseases (NCDs) are the leading cause of mortality and morbidity around the world. Smoking tobacco is one of the important risk factors associated with NCDs, such as cardiovascular diseases and cancer, especially blood and lung cancer (1, 2). Smoking water-pipe is one of the popular forms of consuming tobacco, especially in Middle Eastern countries, such as Iran (3, 4). Previous studies showed that water-pipe in comparison with cigarettes not only produces more volume of smoke, approximately 10 times, but also it contains more nicotine and toxic materials (5, 6). Moreover, the duration of smoking water-pipe is another factor that determines the intensity of its negative effects, such that individuals who start smoking at lower ages are at higher risk of using an illegal drug, alcohol consumption, and deviant behaviors (7, 8). Also, these individuals usually have more difficulty quitting smoking in adulthood (9). Thus, estimating the initiation age and the prevalence of smoking water-pipe along with their associated risk factors are two important parameters for policy-makers to establish preventive policies in the society.

Several studies have been performed on the prevalence and initiation age of smoking water-pipe in Iran; two notable studies were conducted by Nemati et al. (10) and Meysamie et al. (11) based on the (WHO STEPwise approach for non-communicable disease risk factors surveillance) (STEPS) survey, a cross-sectional population-based study. In these studies, they used weighted mean as a measure of prevalence and initiation age of smoking water-pipe. However, regarding the initiation age, the weighted mean is not as informative as using percentiles obtained from the survival analysis where age was considered as follow-up time and starting smoking water-pipe as an event of interest. Another advantage of applying survival analysis in estimating the initiation age of smoking water-pipe is that it considers missing responses as censoring data, which improves the estimations. Furthermore, we could evaluate the effect of independent variables, such as demographic variables on initiation age and calculate the probability of starting smoking at each age. Applying survival analysis in estimating the initiation age of smoking water-pipe has not been considered by researchers. In addition, by considering the cure rate fraction in the survival analysis, we can estimate and evaluate the effect of demographic variables on the prevalence of smoking water-pipe. However, using weighted mean we cannot obtain such information from our study.

In the present study, we introduced a new approach for estimating and evaluating the effect of demographic variables on the initiation age and prevalence of smoking water-pipe. Our approach is based on the survival mixture cure rate model where age is considered as follow-up time and starting smoking water-pipe as an event of interest. The data set used in this study was extracted from the STEPS 2011 survey, a cross-sectional population-based study conducted across the country.

MATERIALS AND METHODS

Data

The data set used in this study was extracted from the STEPS survey conducted in 2011 across Iran (12). This population-based cross-sectional study provides valid information about non-communicable disease risk factors in Iran. The samples were selected from the total country's population based on multistage cluster sampling (12). In this study, we considered individuals who are daily smokers or non-smokers and individuals aged between 16 and 70 years at the time of the study. Initiation age was obtained by gender (men/women) and place of residence (urban/rural). The prevalence of daily smoking of water-pipe was obtained considering gender (men/women), level of education (illiterate/primary/secondary/high-school/associate degree/university), socioeconomic status (low/middle/high), and place of residence (urban/rural).

Statistical Analysis

To estimate the initiation age and prevalence of smoking water-pipe simultaneously, a parametric survival mixture cure model with doubly censoring was applied. In the STEPS data set, some of the participants who are daily smokers did not mention their starting smoking age; thus, their initiation age was considered as left censoring. Right censoring was considered for individuals who are not water-pipe smokers; therefore, censoring time was their ages at the time of the study. Other individuals in the study who were smokers at the time of the study and whose exact ages of their initiation were known were considered as the exact time of the event. This structure of censoring the data set, by which we observe left- and right-censored data along with the exact time of the event is called doubly censoring that was introduced by Turnbull

(13). In summary, we treated missing values or item non-response data as censoring data and considered the age as follow-up time (14). Under the mixture cure rate model (15), the population's survival function is defined as $S_P(t) = \pi + (1-\pi)S^*(t)$, where, $S^*(t)$ is the survival function for susceptible individuals, who experienced the event of interest, π is the proportion of non-susceptible individuals who never experienced the event of interest, and $(1-\pi)$ is the proportion of susceptible individuals (prevalence) (16). We assumed that the survival time for susceptible individuals followed $Weibull(\mu, \lambda)$ distribution, where, μ and λ represent the shape and scale parameters, respectively. The appropriateness of the Weibull distribution was checked by comparing the model fitted cumulative curves with observed cumulative curves as shown in Figure 1. Evaluation of the effect of demographic variables, including sex and area of residence on the initiation age was conducted using the log link function of scale parameter λ of Weibull distribution as $\log(\lambda) = \beta_0 + \beta_1.sex + \beta_2.Area$.

The effect of demographic variables including sex, area of residence, level of socioeconomic status, and level of education on the parameter π was evaluated using logistic regression with logit link function as follows:

$$logit(\pi) = \alpha_0 + \alpha_1.sex + \alpha_2.SES + \alpha_3.Education + \alpha_4.Area$$

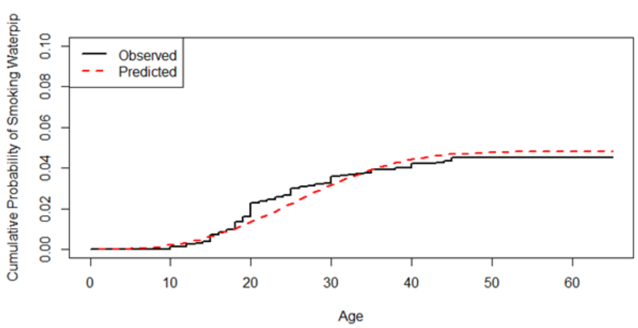

Figure 1. Cumulative Probability of smoking water-pipe initiation age estimated based on Turnbull method (Black-line) and the proposed model (Red-line)

Advances in computing power and available software have made Markov chain Monte Carlo (MCMC) (17, 18) one of the most important computational tools in Bayesian analysis, especially in survival model with mixture cure rate fraction. In our approach, we used MCMC via a Metropolis-Hasting algorithm for sampling from the posterior distribution of parameters with the zero tricks for arbitrary likelihood in OpenBUGS (19) software. Under the fully Bayesian approach, we set a non-informative prior distribution for the model's parameters as the normal distribution with zero means and precision of 0.0001 was assumed for the survival and logistic regression parameters. Gamma (0.0001, 0.001) prior distribution was set for the shape parameter of the Weibull distribution. In summary:

$\beta_l \sim N(0,0.001), l = 0,1,2$

$\alpha_l \sim N(0, 0.001), l = 0,1,2,3,4$

$\mu \sim Gamma(0.001,0.001)$

To incorporate the survey weights into the analysis, we used the Bayesian Pseudo-Posterior Estimator (BPPE) method (20), in which we replaced the likelihood with pseudo-likelihood in the usual formula of Bayes' theorem. The statistical methodology of our approach is explained in detail by Turnbull, Achcar et al. and Gunawan (13, 16, 20). The final analysis was based on the complete case of the data set. The convergence of MCMC chains was checked by the coda package using R software. All statistical analyses were performed by OpenBUGS version 3.2.3 and R version 3.5.1

RESULTS

From the 9764 study population, there were 5709 (58.5%) women and 4055 (41.5%) men with the mean±SD age of 38.9±15 years (ranging from 16 to 65 years old). Totally, 9410 (96.4%) participants of the study population did not experience water-pipe smoking until the time of the study. On the other hand, 354 (3.6%) were daily smokers, of whom 39 (11%) did not mention their age of smoking onset. Most of the participants lived in urban areas (69.8%). The highest percentage of participants' educational level was high school or less (85.5%). At the time of the study, 22.2% of participants were older than 55 years old and 29.1% were younger than 27 years old. Demographic characteristics of water-pipe smokers and non-smokers along with numbers and the percentage of missing data per variable are provided in Table 1.

The observed cumulative curve based on the Turnbull method and predicted probability curves of starting smoking water-pipe based on the proposed model are shown in Figure 1. From this figure, a good agreement between predicted and observed cumulative probability curves of starting smoking water-pipe could be concluded.

Estimation of the model parameters is presented in Table 2. Based on the credible interval of model parameters in Table 2, there was no difference between the initiation age of smoking water-pipe in men and women (HR=1.07, 95% CI: 0.76- 1.58), but there was a significant difference between the initiation age in urban and rural areas (HR=0.62, 95% CI: 0.44- 0.88). Regarding the prevalence of smoking water-pipe, there was a significant difference between the odds of smoking water-pipe between men and women (OR=2.34, 95% CI: 1.79- 3.7), and also a significant association was observed between socioeconomic status and prevalence of smoking water-pipe (OR=0.84, 95% CI: 0.72- 0.97). However, there was no significant association between educational level (OR=1.06, 95% CI: 0.97- 1.15) and area of residence (OR=1.2, 95% CI: 0.93- 1.57) with odds of smoking water-pipe.

Table 1. Demographic characteristics of studied population according to water pipe smoking status

Characteristics		Total (%)	Water pipe smoker	
			No (%)	Yes (%)
Gender[1]	Women	5709 (58.5%)	5534 (58.8%)	175 (47.6%)
	Men	4055 (41.5%)	3876 (41.2%)	179 (52.4%)
Location of Residency[2]	Urban	6813 (69.8%)	6583 (70%)	230 (65%)
	Rural	2951 (30.2%)	2827 (30%)	124 (35%)
Education[3]	Illiterate	2007 (20.6%)	1903 (20.2%)	104 (29.4%)
	Primary	2048 (21%)	1976 (21%)	72 (20.4%)
	Secondary	1775 (18.2%)	1702 (18.1%)	73 (20.6%)
	High school	2510 (25.7%)	2429 (25.8%)	81 (22.9%)
	Associate	533 (5.5%)	523 (5.6%)	10 (2.8%)
	University	891 (9%)	877 (9.3%)	14 (3.9%)
Socioeconomic status[4]	Low	3025 (30%)	2882 (30%)	115 (34.2%)
	Meddle	3381 (35%)	3268 (35%)	152 (45.3%)
	High	3358 (35%)	3260 (35%)	69 (20.5%)
Age Group[5]	16-26	2843 (29.1%)	2723 (26.1%)	120 (33.9%)
	27-37	2242 (23%)	2166 (24.2%)	76 (21.5%)
	38-54	2510 (25.7%)	2428 (25.3%)	82 (23.1%)
	55-65	2169 (22.2%)	2093 (24.4%)	76 (21.5%)
Total		9764	9410 (96.4%)	354 (3.6%)

[1]Missing: n=0 (0.0%). [2]Missing: n=0 (0.0%). [3]Missing: n=7 (0.07%). [4]Missing: n=36 (0.37%). [5]Missing: n=0 (0.0%)

Table 2. Estimation of model parameter for initiation age and prevalence of smoking water pipe

		Initiation age Hazard Ratio (95% CI) in smokers	Smoking prevalence Odds Ratio (95% CI)
Gender	Women	Ref.	Ref.
	Men	1.07 (0.76,1.58)	2.34 (1.79-3.7)*
Area of Residence	Rural	Ref.	Ref.
	Urban	0.62(0.44,0.88)*	1.2 (0.93,1.57)
Education		-	1.06 (0.97,1.15)
Socioeconomic status		-	0.84 (0.72-0.97)*

Estimated value for shape parameter is 2.92 (95% CI: 2.68, 3.17)

The estimated mean and median age of smoking water-pipe based on our approach were 25.82 (95% CI: 24.13- 27.63) and 26.11 (95% CI: 24.42- 28.02) years old, respectively. The median and mean initiation age of smoking water-pipe in rural areas were 23.06 (95% CI: 21.14- 25.36) and 23.32 (95% CI: 21.43- 25.6) and in urban areas were 27.1 (95% CI: 24.96- 29.58) and 27.4 (95% CI: 25.29- 30.03), respectively. Based on the model results, smokers in rural areas approximately start smoking water-pipe four years earlier in comparison with smokers in urban areas. The estimated prevalence of water-pipe smoking in total, men, and woman were 4.8% (95% CI: 4.19%- 5.51%), 7.77% (95% CI: 6.76%- 8.86%), and 3.47% (95% CI: 2.8%- 4.25%), respectively. Among the susceptible individuals, the probability of starting smoking in each age range is reported in Table 3.

Table 3. Probability of starting smoking water-pipe in different age range in susceptible individuals

Age Range	Percentage of starting smoking among susceptible individuals	95% Credible interval
0-10	4.2%	2.63% , 5.24%
10-20	23.78%	16.83% , 25.72%
20-30	37.82%	30.67% , 39.8%
30-40	25.84%	23.98%, 30.51%
40-50	7.46%	5.9%, 14.84%
50>	0.85%	0.45%, 4.83%

DISCUSSION

In the current study, a new approach based on a parametric survival mixture cure rate model with doubly censoring was used to simultaneously estimate and evaluate the effect of demographic variables on initiation age and prevalence of smoking water-pipe. In this approach, we considered age as follow-up time and starting smoking water-pipe as an event of interest. To the best of our knowledge, this is the first study with such an approach for estimating the initiation age of smoking water-pipe. This approach could be used as a framework for the analysis of similar data set in future studies.

It was reported that women start smoking at later ages compared with men (21). However, in our study, we did not observe a significant difference between the initiation age of smoking water-pipe in men and women (HR= 1.07, 95% CI: 0.76- 1.58). This could be as a result of cultural perception about water-pipe smoking, which is not as negative as cigarette smoking. We observed a significant difference between initiation age in urban and rural areas (HR=0.62, 95% CI: 0.44- 0.88), such that the hazard of smoking in urban areas is 38% lower than in rural areas. Furthermore, we estimate that smokers in rural areas start smoking approximately four years earlier than urban smokers. This finding is based on the accelerated failure time assumption (AFT) property of the Weibull distribution in survival analysis (22). Unfortunately, there is no similar study on smoking water-pipe to compare with. The estimated mean age of starting smoking in the total population based on the survival model was 25.82 (95% CI: 24.13- 27.63) years old, whereas the mean initiation age estimated based on the weighted mean method was 23.72 (95% bootstrap confidence interval: 22. 08, 25.53) years. This underestimation of initiation age is caused by eliminating censoring data in the weighted mean approach. However, this bias in estimation is treated appropriately using survival analysis. Table 3 is more informative because it provides more information in addition to the mean initiation age. This table shows that the majority of smokers start smoking at the age range of 20 to 30 years (37.82%, 95% CI: 30.67- 39.8) and then at the age range of 30 to 40 years old (25.84, 95% CI: 23.98- 30.51). Notably, these percentages are different from the prevalence of smoking at each age range. Regarding the former observation, we estimated the exact age of starting smoking water-pipe, regardless of their age at the time of their participation in the study. Additionally, based on the median initiation age in 2011, 50% of smokers started smoking at the age of younger than 26.11 (95% CI: 24.42- 27.02) years. Thus, this age is more informative for establishing preventive policies. In the study by Aryanpur et al. (23), which was based on the STEPS 2011 and using net probability, the probability of smoking cigarettes in men attains its maximum at 30 years and then decreased to zero at 45 years. However, there is no similar study on smoking water-pipe.

Regarding the prevalence of smoking water-pipe, the logistic part of the proposed model estimates and evaluates the effect of demographic variables on the prevalence of smoking. Applying logistic regression for accessing the effect of independent variables on the prevalence of smoking water-pipe and cigarette is popular (10). From the logistic parts of the proposed model, we observed that the odds of smoking water-pipe in men was 2.34 (OR=2.34, 95% CI: 1.79- 3.7) times more than the odds of smoking in women, and with one level increase in socioeconomic status the odds of smoking water-pipe 16% decreased (OR=0.84, 95% CI: 0.72- 0.97). However, we did not observe an association between smoking water-pipe and area of residence (OR=1.2, 95% CI: 0.93- 1.57) and level of education (OR=1.06, 95% CI: 0.97- 1.15). Furthermore, based on the results of the logistic regression, the prevalence of smoking in total, men, and women were 4.8% (95% CI: 4.19%- 5.51%), 7.77% (95% CI: 6.67- 8.86-), and 3. 47% (95% CI: 2.8- 4.25-), respectively. In the study by Meysamie et al. (11) on similar data set, they reported that the prevalence of smoking water-pipe in total, men, and women were 3.6% (95% CI: 3.2-4.1%), 4.9% (95% CI: 4.2-5.8%), and 2.3% (95% CI: 1.9-2.7%). Such underestimation of the prevalence in Meysamie et al. (11) study in comparison with our estimation is generated from the censoring used in our study, especially right censoring because our model jointly estimates the prevalence and initiation age of smoking water-pipe. Also, Meysamie et al (11) reported the equal prevalence in rural (3.6%; 95% CI: 2.9-4.4) and urban (3.6%; 95% CI: 3.1%, 4.2%) areas, which is consistent with our findings. Regarding socioeconomic status, our findings are consistent with those reported in the study by Ghelichkhani et al.(24), in which the prevalence of water-pipe smoking was lower in a higher socioeconomic group compared with a lower socioeconomic group. Regarding educational level, although we did not observe significant differences between odds of smoking water-pipe in different educational levels; in a study by Danaei et al. (25) conducted in southeast Iran (recruiting 1090 adult in their study) in 2016, a significant relationship was reported between educational level and smoking water-pipe, such that with increasing the level of education, the likelihood of smoking increased. This inconsistency between the findings can be as a result of the difference between the location and time of the studies (25).

In conclusion, for the first time, we used survival analysis to estimate the initiation age of smoking water-pipe and evaluated the effects of demographic variables at this age. Survival analysis is a powerful statistical method for analyzing time-to-event data. Furthermore, by considering cure fraction in survival analysis, we could estimate the prevalence of smoking water-pipe and evaluate the effect of demographic variables on this important index. Our survival model was based on a parametric survival model and our estimation method was based on the Bayesian MCMC method, which is useful when the rate of censoring is high and the model is complicated by doubly censoring and mixture cure rate model. Although considering survey weight in Bayesian estimation is not popular and the methodology of this topic is open, Gunawan (20) recently introduced two methods for considering survey weight in Bayesian estimation. The first method is Bayesian Pseudo-Posterior Estimator (BPPE), which is useful for large sample size data and the other one is based on the bootstrap resampling and data augmentation method, which is useful for small sample size data set, especially because of the issue of longer computational time. One limitation of our study was that we did not consider the educational level and socioeconomic status in the survival regression part of the model because we did not know the exact level of education and socioeconomic status at the time of starting smoking water-pipe for smoking individuals in the STEPs data set.

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