Journal of Biostatistics and Epidemiology

J Biostat Epidemiol. 2022;8(4):452-464

Original Article

An Integrative Bayesian Model Analysis of Patient Characteristics and Treatment Variables to Understand Lung Cancer Survival Rates in Kerman Province, Iran

Javad Ghasemi[1,2], Mitra Samareh Fekri[3], Mohammad Hasan Larizadeh[4], Shahriar Dabiri[5], Yunes Jahani[2,6]

[1]HIV/STI Surveillance Research Center, and WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran.
[2]Department of Biostatistics and Epidemiology, School of Public Health, Kerman University of Medical Sciences, Kerman, Iran.
[3]Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran.
[4]Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of medical sciences, Kerman, Iran.
[5]Pathology and Stem Cell Research Center, Department of Pathology, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran.
[6]Modeling in Health Research Center, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran.

ARTICLE INFO

Received 04.09.2022
Revised 25.09.2022
Accepted 17.11.2022
Published 15.12.2022

Key words:
Lung cancer;
Bayesian;
Survival rate

ABSTRACT

Introduction: Lung cancer (LC) is the most common type of cancer and causes of death among males. This study aims to estimate the survival rate of lung cancer patients by employing the benefits of Bayesian modeling in determining factors affecting the survival of lung cancer in Kerman province, Iran.
Methods: We conducted a historical cohort study of 195 patients with lung cancer from 2016 to 2018. In this study, we used linear dependent Dirichlet process (LDDP), and employed some results of the previous study as informative prior for better estimation.
Results: Of the 195 patients, 160 died. The mean age of patients at the time of diagnosis was 62.43±12.55. The median survival time of patients was 10.4 months. Men accounted for 75.9% of the total patients. One, two, and three-year survival rate was 44.5%, 22.9%, and 16.4%, respectively. The multivariable model results showed that treatments were significant. Other variables had no significant effect.
Conclusion: Our study highlights the importance of prompt diagnosis and appropriate treatment in improving the survival rate of lung cancer patients. We found that patients who received at least one usual lung cancer treatment, such as chemotherapy, radiation therapy, or surgery, had higher survival rates compared to those who did not receive any treatment. While our study has some limitations, such as its retrospective design, our use of Bayesian modeling techniques allowed us to effectively incorporate prior information from previous studies to improve estimation accuracy.

*.Corresponding Author: u.jahani@kmu.ac.ir

Introduction

Cancer is one of the most dangerous non-communicable diseases worldwide. In 2018, 18.1 million new cancer cases and 9.6 million cancer deaths were reported from 185 countries.[1, 2] Cancer is the third leading cause of death after heart disease and car accidents in Iran.[3, 4]

Lung cancer is by far the leading cause of cancer death among both men and women, approximately 20% of all cancer deaths.[2]

More than half of new lung cancer cases occur in developing countries, such as Iran.[5] Lung cancer incidence is significantly increasing in Iran, which causes death in 9.8% of men and 6.7% of women in 2012.[6]

The survival rate of people with lung cancer is lower than other cancers such as stomach, colon, or breast.[7] Patients have a 10% to 13% probability of surviving for five years after diagnosis.[8, 9]

There are two types of lung cancers, determined by the type of cells in the lung tissue: small cell carcinoma (SCC) and non-small cell lung cancer (NSCC).[10] Non-small cell carcinoma is more prevalent than small cell carcinoma (about 85% of lung tumors[11]) and has slower expansion and growth. SCC is divided into three subcategories according to the type of cell in which cancer develops: Squamous Cell Carcinoma (also noted Epidermoid Carcinoma), Adenocarcinoma, and large cell carcinoma.[12]

Different factors can increase the risk of lung cancer, the most common of which is smoking.[11, 13, 14] Surveys have also shown that consuming opium or its derivatives can enhance the risk of lung cancer.[15, 16] The prevalence of opium uses among the adult population in Kerman, a southeastern province in Iran, is 11% to 15%.[16, 17]

Lung cancer treatment is determined by various factors, including the type of cancer, the size, area, and spread of the tumors, and the patient's overall health. Different and combined treatments are applied to deal with lung cancer to improve the patient's quality of life or reduce symptoms. Surgery, chemotherapy, and radiotherapy are some of the most common lung cancer treatments.[18] The objective of this research was to investigate the factors that can affect the survival rate of lung cancer among patients in Kerman province, Iran, utilizing Bayesian modeling techniques to incorporate prior information from previous studies and identify factors that affect survival outcomes. By investigating these factors, we hope to contribute to a better understanding of lung cancer management in this region and provide insights that could inform future research and policy decisions.

Methods

This study was a historical cohort conducted in Kerman province, Iran. In September 2020, we collected information from 195 patients through medical histories and telephone interviews with the patient or one of their immediate family (in case of death or weakness) diagnosed with lung cancer through pathological tests between March 20, 2016, to March 20, 2018. To analyze the impact of demographic and clinical factors on survival time among lung cancer patients, we used Bayesian regression methods. After an extensive review of the literature,[19-22] we selected the Linear Dependent Dirichlet Process (LDDP) as our non-parametric Bayesian model, which can handle different types of survival data and cluster individuals

with similar survival patterns We also noted that this Bayesian regression method can be a suitable technique to examine the direct effect of a variable on survival when proportional hazards (PH) assumption is not met.[23]

Although Bayesian methods have some advantages over classical statistical methods, such as the ability to incorporate prior information into the analysis and flexibility in model specification, they rely on certain assumptions that must be carefully considered. Specifically, Bayesian models require the specification of prior, which can be influenced by informative or subjective priors. Moreover, the choice of prior can impact the results of the analysis. To address this concerns, we conducted sensitivity analyses to evaluate the impact of key assumptions and modeling choices on our findings.[24, 25]

To incorporate informative priors into our analysis based on our existing knowledge about the parameters of interest, we carefully selected prior distributions that reflected our beliefs about the underlying structure of the data before the new data were observed. For this purpose, we relied on several references in Bayesian data analysis.[21, 26-28]

We acknowledge that some patients in our study may have died from non-lung cancer-related causes, and therefore assumed that all such deaths were due to non-cancer-related causes and censored them. Specifically, eight patients were censored due to death from other causes. To account for competing risks, we also conducted sensitivity analyses using the Fine and Gray method.[29, 30] These analyses produced similar results to our main analysis, suggesting that the assumption of non-informative censoring did not significantly affect our findings.

We used the date of lung cancer diagnosis as the reference point to calculate the start time for each patient in our cohort. For those who died during the study period, their stop time was defined as the date of death. For those still alive at the end of the study period or who died from causes other than lung cancer, their stop time was defined as the date of last follow-up. We also used Kaplan-Meier survival analysis to estimate overall survival rates for the cohort and generalized Wilcoxon test results to compare survival curves between different groups. We conducted multivariable regression analysis included Smoking status, type of lung cancer, and treatment modality as the covariates, using LDDP models.

Ethical issues

The Ethics Committee of Kerman University of Medical Sciences approved the study protocol (Ethics code No: IR. KMU. REC.1398.418). We got verbal informed from participants and told them the study's general objectives and the potential re-use of the research data participants. We also confirmed that all methods were performed by the relevant guidelines and regulations.

Measures

In this study, the age, gender, habitat, family history of cancer smoking and opium status, treatment, and histology of cancer were our independent variables, and time to event as the dependent variable was the interval time from diagnosis until death.

Data analysis

This study initially used Kaplan–Meier and

Generalized Wilcoxon methods to estimate and compare survival rates. We used the LDDP to investigate the effect of variables on survival time.[23] This model is one of the Bayesian regression methods and a generalization of the AFT model that is useable and has some advantages when proportional hazards are not met.[21, 31, 32] We tested the proportional hazards assumption using the Schoenfeld Residuals test, which showed that smoking (P-value = 0.03) and treatments (P-value = 0.001) do not have proportional hazards. Therefore, using classical models cannot determine the direct effect of these two variables, so the LDDP model could be an appropriate choice.

We used the univariate and multivariable models to detect influential variables. For multivariable models, we first set several models (each one has a different combination of independent variables). Then we compared models based on Log pseudo marginal likelihood (LPML) and chose the best and final model. We carried out data analysis by utilizing the R program with the "DPpackage" package.

Results

Among 195 patients with lung cancer, 160 (82.1%) patients died due to lung cancer, eight patients (4.1%) died because of other causes of death, and 27 patients (13.8%) were alive at the end of the study. The mean age of patients at the time of diagnosis was 62.43±12.55 years (range; 19-90). 80 (41%) patients were older than 64 years old. The median survival times after diagnosis were 309 days.

Table 1 contains the descriptive statistic and the results of the Generalized Wilcoxon test. Also, Figure 1 shows the overall survival of patients by the Kaplan–Meier method. Based on the Generalized Wilcoxon p-value, it is visible that smoking, opium consumption, and treatment have a significant effect on survival time.

The results of the univariate model are reported in Table 2. According to the Credible Interval reported in Table 2, the only significant variable is treatment.

According to multivariable model results (Table 3), we realized treatments had a significant effect on increasing patient survival rate; also,

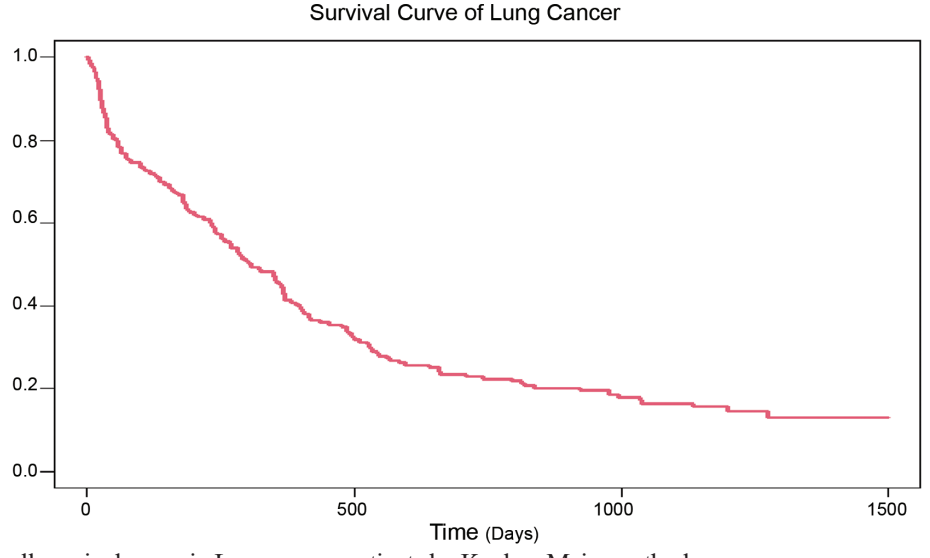

Figure 1. The overall survival curve in Lung cancer patients by Kaplan–Meier method

Table 1. Descriptive statistics and Lung cancer patient's characteristics with 1, 2 and 3-year overall survival in Kerman Province between 2016-2019

Variables	Alive n (%)	Dead n (%)	1-Year OS (%)	2-Year OS (%)	3-Year OS (%)	Median survival (days)	Generalized Wilcoxon P-value
Overall survival of all patients	35 (17.9)	160 (82.1)	44.5	22.9	16.4	309.0	-
Age (year)							0.12
≤64	25 (21.7)	90 (78.3)	48.0	26.3	20.4	254.0	
>64	10 (12.5)	70 (87.5)	39.4	18.0	10.0	351.0	
Gender							0.26
Male	21 (14.2)	127 (85.8)	41.3	19.0	12.0	366.0	
Female	14 (29.8)	33 (70.2)	54.1	34.4	29.1	298.5	
Habitat							0. 69
Urban areas	21 (15.4)	115 (84.6)	44.5	21.2	15.5	320.0	
Rural areas	14 (23.7)	45 (76.3)	44.6	27.5	18.8	280.0	
Family history of cancer							0.58
No	28 (16.5)	142 (83.5)	42.8	22.1	16.1	305.5	
Yes	7 (28.0)	18 (72.0)	57.3	29.7	19.8	366.0	
Smoking status							0.005
No	26 (32.1)	55 (67.9)	58.2	37.6	33.1	405.0	
Yes (only before diagnosis)	8 (8.3)	88 (91.7)	31.6	10.3	4.5	235.5	
Yes (before and after diagnosis)	1 (5.6)	17 (94.4)	49.8	22.0	-	382.5	
Opium status							0.03
No	24 (25.8)	69 (74.2)	52.1	32.2	27.0	366.0	
Yes (only Before diagnosis)	9 (21.4)	33 (78.6)	43.2	21.4	12.7	232.5	
Yes (before and after diagnosis)	2 (3.3)	58 (96.7)	33.0	8.9	-	239.0	
Treatment							0.005
No	11 (16.9)	54 (83.1)	29.5	17.9	14.3	72.0	
CT	11 (15.9)	58 (84.1)	42.1	19.4	13.4	257	
S	4 (51.7)	3 (42.9)	66.7	50.0	50.0	523	
CT+RT	0 (0)	28 (100)	53.6	10.7	-	366	
CT+S	4 (44.4)	5 (55.6)	64.0	40.0	40.0	525	
CT+RT+S	5 (29.4)	12 (70.6)	70.2	51.1	36.9	530	
Histology							0.19
Small cell carcinoma	0 (0)	22 (100)	27.2	4.5	-	196.0	
Adenocarcinoma (NSCLC)	6 (12.8)	41 (87.2)	52.3	26.0	12.5	366.0	
Squamous cell carcinoma (NSCLC)	4 (12.5)	28 (87.5)	42.3	16.1	9.4	268.0	
Large cell carcinoma (NSCLC)	0 (0)	4 (100)	25.0	-	-	121.0	
Lung NOS	25 (27.7)	65 (72.3)	46.1	29.6	27.0	326.0	

OS, Overall Survival; (-) Uncountable; RT, Radiotherapy; CT, Chemotherapy; S, Surgery

Table 2. Determining the influencing factors on the survival rate by using the univariate Bayesian regression model

Characteristic	Model coefficients	St. Err.	Exp (β)	95% CI Exp (β)
Age(year)				
≤64	reference		1	
>64	0.34	0.37	1.41	(0.68, 2.94)
Sex				
Male	reference			
Female	0.22	0.4	1.25	(0.63, 2.72)
Habitat				
Urban areas	reference			
Rural areas	0.02	0.33	1.02	(0.53, 1.93)
Family history of cancer				
No	reference			
Yes	0.17	0.38	1.18	(0.58, 2.55)
Smoking status				
No	reference			
Yes (only before diagnosis)	-0.59	0.46	0.55	(0.22, 1.43)
Yes (before and after diagnosis)	-0.3	0.53	0.74	(0.35, 2.05)
Opium status				
No	reference			
Yes (only Before diagnosis)	-0.2	0.38	0.82	(0.38, 1.68)
Yes (before and after diagnosis)	-0.58	0.46	0.56	(0.22, 1.29)
Treatment				
No	reference			
CT	0.84	0.45	2.32	(1, 5.64)
S	0.55	0.76	1.73	(0.39, 7.77)
CT+RT	1.32	0.46	3.74	(1.48, 9.39)
CT+S	1.15	0.73	3.16	(0.71, 12.3)
CT+RT+S	1.42	0.52	4.14	(1.48, 11.02)
Histology				
Small Cell Lung Cancer	reference			
Non-Small Cell Lung Cancer	0.47	0.33	1.59	(0.83, 3.06)
Lung NOS	0.48	0.44	1.61	(0.7, 4)

CI, Credible Interval

the result showed that smoking and cancer type did not have a significant effect.

According to multivariable model, the median survival time of patients who received chemotherapy was 2.81 months (95% CI: (1.12, 4.62)), higher than patients who did not have any treatment. Also, patients who had chemotherapy and radiotherapy; had a median survival time of 3.53 months (95% CI: (1.42, 8.49)) higher than patients who did not have any treatment; as the same way, patients who had chemotherapy and surgery had a median survival time of 5.99 months (95% CI: (1.43, 25.53)) higher than patients who did not have any treatment. Also, patients who underwent three treatments simultaneously (chemotherapy, radiotherapy, and surgery) had a median survival time of 5.53 months (95% CI: (1.72, 19.29)) higher than patients who did not have any treatment. Table 3 shows the multivariable model results. Also, Figure 2 includes survival diagrams produced by the model and Kaplan–Meier for variables such as cancer type, smoking, and treatment which shows the effect of each variable on increasing or decreasing the survival rate. For example, in the chart related to smoking, it can conclude that smokers' survival rate (Smoking before the diagnosis of cancer or before and after diagnosis) decreases earlier than non-smokers. However, those differences were not significant.

Table 3. Determining the influencing factors on the survival rate by using the Multiple Bayesian Regression Model

Characteristic	Model coefficients	St. Err.	Exp (β)	95% CI Exp (β)
Smoking status				
No	reference			
Yes (only before diagnosis)	-0.58	0.37	0.55	(0.27, 1.2)
Yes (before and after diagnosis)	-0.32	0.53	0.72	(0.26, 2)
Histology				
Small Cell Lung Cancer				
Non-Small Cell Lung Cancer	0.59	0.35	1.8	(0.91, 3.52)
Not specified	0.47	0.39	1.59	(0.76, 3.49)
Treatment				
No				
CT	0.82	0.36	2.27	(1.12, 4.62)
S	1.53	1.38	4.62	(0.38, 87.35)
CT+RT	1.26	0.45	3.53	(1.42, 8.49)
CT+S	1.79	0.74	5.99	(1.43, 25.53)
CT+RT+S	1.71	0.61	5.53	(1.72, 19.29)

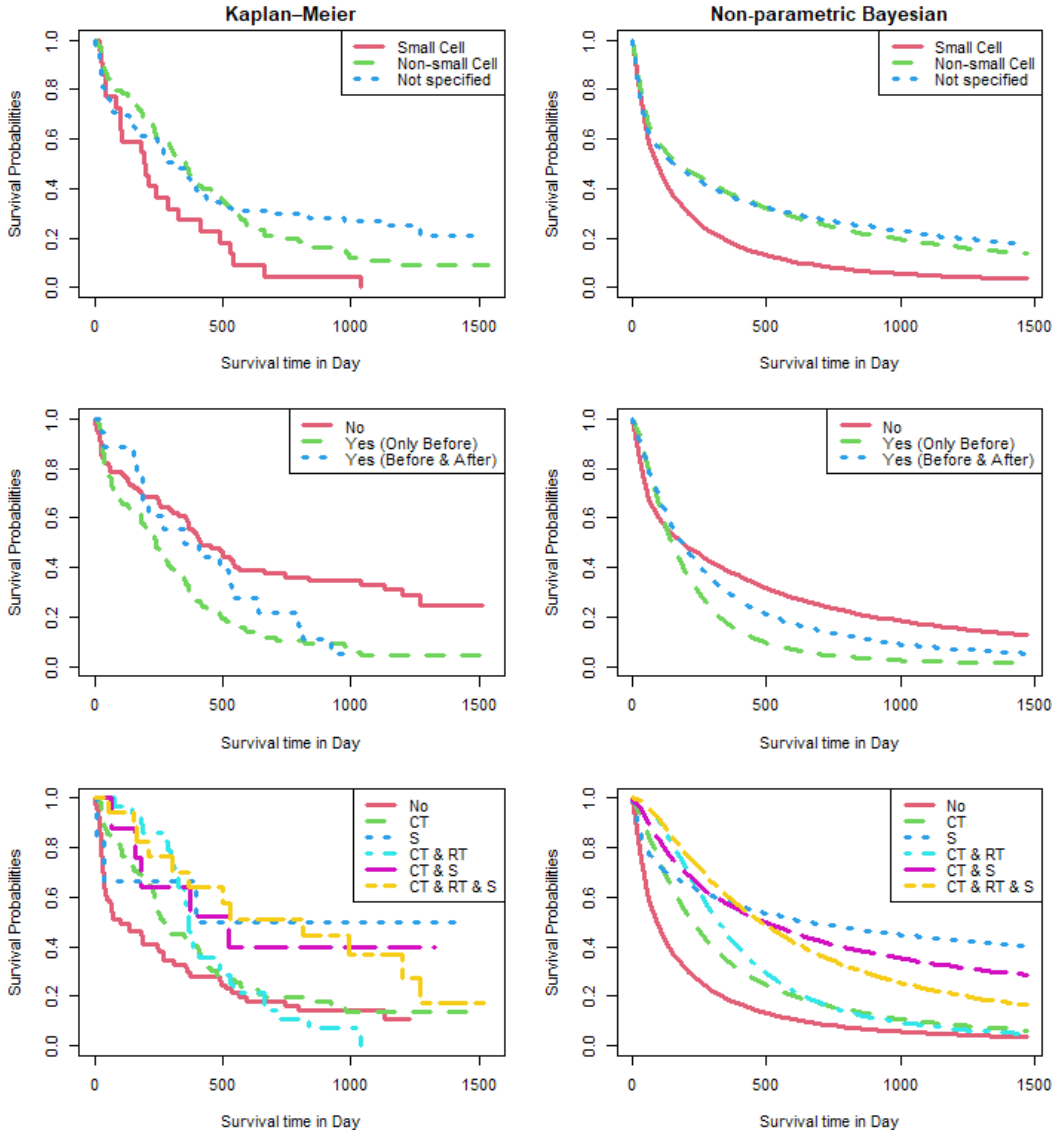

Figure 2. The panels from top to bottom are survival probability according to Lung cancer cell type, Smoking status, and type of treatment, respectively. The left panels represent the Kaplan–Meier diagram of each variable and the Right's are derived from the nonparametric Bayesian multivariate model.

Discussion

There are several models available for analyzing survival data with non-proportional hazards, such as extended Cox regression or flexible parametric models. However, we chose to use LDDP to investigate the factors affecting lung cancer patients' survival rates. The model was chosen because it can accommodate non-proportional hazards and provide more flexibility in modeling time-to-event data. In this study, the proportional hazards assumption for smoking and type of treatment, which were two main variables, was not held. So, the use of the LDDP to investigate directs effect of these variables on patients' survival was the right choice.

But, it is important to note that each model has

its own strengths and limitations, and different models may be more appropriate for different research questions and types of data. Therefore, researchers should carefully evaluate the assumptions and limitations of available models and select an appropriate model based on their specific research question and data characteristics.

Based on our study, the mean age of patients was 62.43 years. In other studies, run in Iran, the mean age at the time of diagnosis was 62.86, 63.12, and 60.57 years which were compatible whit our finding.[1, 33, 34] In a survey conducted in the United States, the mean age of patients was 66.9 years at the time of diagnosis.[35] This difference shows that the age of patients in our study is lower than in the US.

In this study, most of the patients were male (75.9%). This result is in line with Salehi et al., Baba Nejad et al., and Biswas T et al. which 83.5%, 70%, and 62.6% of the study population were male, respectively. So, we found a significantly higher lung cancer incidence rate among men.[1, 34, 35]

The median survival time and the 3-year survival rate of patients was 10.4 months, and 16.4%, respectively, which shows the low survival rate of patients with lung cancer. Other studies had similar results; for example, in another survey in Iran, the three-year survival rate of patients was 16%.[36] Lachgar A et al. reported 6.1% for three-year survival rate for patients;[37] and in Ozlu's study, the 5-years survival rate of patients with lung cancer was 10%.8 The different survival rates in various studies can depend on the time of diagnosis, disease severity, proper and timely treatment, and patient's condition during treatment or other factors.

Based on the results, it can conclude that the usual treatments in patients with lung cancer have a positive and significant effect on the survival rate of patients. So, it is important to diagnosis cancer timely, and patients receive appropriate treatment. Like other studies, this study showed that the median survival time of people who received a combination of three surgical, chemotherapy, and radiotherapy treatments are longer than other patients.[38-40]

According to this study's results and survival plots, patients who undergo chemotherapy have better 1-year survival than those with no treatment.

In this study, opium consumption harmed the survival rate, but this effect was not significant, and we did not use opium consumption in the multivariable model. Also, the smoking effect in multivariable model was not significant, while smoking is one of the leading causes of lung cancer.[41, 42] This result may be due to the low survival of patients with lung cancer. These results were consistent with Biswas T et al.[35] The study's results show that age, sex, and type of tumor had no significant effect on patients' survival rate. These results were consistent with Kumar's study et al., which was performed on lung cancer patients' survival by applying a parametric Bayesian Accelerated failure time model (AFT) with a log-logistic density function.[43]

In this study, survival rates were different according to the type of tumor, so that people with SCLC tumors had lower survival rates than those with NSCLC tumors, but this difference was not significant. Similar studies had similar results.[35, 44]

Conclusion

Treatment can significantly improve patients'

survival status. Thus, prompt diagnosis and treatment immediately are essential. The combination of chemotherapy with radiation therapy and surgery can play a substantial role in improving patient survival. So patients shouldn't hesitate to undergo this treatment if possible, depending on their health status. It is recommended that patients stop smoking and opium consumption after diagnosis because the utilization of these substances can have a devastating effect on the patients' progress and get their health status worsened. On the other hand, our analysis suggests that the Bayesian approach can be a valuable tool for modeling complex systems with limited data, but it still relies on certain assumptions and prior knowledge. Therefore, it should be used judiciously in situations where it offers advantages over classical statistics, such as providing more flexibility in the modeling process.

Acknowledgment

We want to express our gratitude to all personnel and patients of teaching hospitals in Kerman and Kerman University of Medical Sciences, who helped to handle the present study.

Conflict of Interests

The authors declare they have no competing interests

Abbreviations

LC, Lung Cancer
SCC, Small Cell Carcinoma
NSCC, Non-Small Cell Lung Cancer
PH, Proportional Hazards
LDDP, Linear Dependent Dirichlet Process
AFT, Accelerated failure time
LPML, Log pseudo marginal likelihood
SCLC, Small Cell Lung Cancer
NSCLC, Non-Small Cell Lung Cancer

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