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A Comparative Study of Survival approaches for Breast Cancer Patients

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Abstract: A survival analysis model leads one to analyze main factors which impact a patient's therapy process. In practice a survival analysis is capable of affecting therapeutic protocols. Different methods have been approached to analyze the survival of a breast cancer patient by researchers. The objective of this research is to lead specialists analyzing the breast cancer patients effectively. This research by analyzing 2010 breast cancer patients 1) attempts to propose six different statistical models using parametric and semi-parametric approaches for survival analysis of breast cancer patients, 2) compares the performance capabilities of the proposed statistical models analytically, and 3) addresses the most superior approach for a survival analysis of a breast cancer. To analyze the capability of the six proposed models Akaike term is used. This comprehensive research also indicates that the hazard factors commonly proposed in literature are not capable of leading a specialist to analyze the survival completely. Although it is possible to model the breast cancer survival using different approaches, this research reveals the proposed semi parametric model is capable of providing the most superior condition. The capability of the best parametric model among the five proposed parametric models of this comprehensive research is also addressed. Kaplan-Meier diagram is used to analyze the importance of two new hazard factors proposed in this paper.

Keywords: Survival Analysis, Breast Cancer, Cox Regression, Semi Parametric Model

1. Introduction

Literature indicates that breast cancer is one the most common cancer among women. Hence survival analysis of breast cancer is referred to as an important issue for physicians. Literature addresses that several different researchers have contributed to the survival rate of breast cancer. The first aim of a survival analysis is to design an empirical model. This empirical model is capable of predicting patients longevity based on explanatory variables of the model which actually influence on a patient's longevity [1]. Survival models are allowed to estimate the death time of patients using statistical analysis as well as determination of the most important impressive variables on a patient's survival. In this analysis type the response variable may be the time of death, disease recurrence, or metastasis of breast cancer. Literature addresses that three statistical approaches are used to analyze survival data: 1) Cox proportional hazards as a semi-parametric [2], 2) parametric functions such as Weibull, exponential, Gompertz, log-normal, and log-logistic log [1], and 3) nonparametric approach such as Aalen's additive risk model and Kaplan-Mayer graph [3].

In the case that a parametric model is approached, it means that the patient's survival time follows a known distribution. In this case, maximum likelihood is usually used for estimation of unknown parameters. The following weaknesses of parametric models are addressed by literature [4]:

1) A parametric model includes more assumptions compared to a semi-parametric or a nonparametric type.

2) In the case of existing right censored data, it necessarily does not provide a better response compared to other approaches.

3) For estimation of a survival function, a probability density function should be approximated.

Vallinayagam et al. [5] considered 686 breast cancer patients and compared different parametric models for the survival analysis. They concluded that log-normal is the most superior compared to the parametric models used in their research. Literature indicates that although nonparametric models does not necessarily consider an assumed distribution [6], the approach has less capability of characterizing significant effects of variables simultaneously compared to other models. In this approach practically some data are missed [6-9]. Cox semi-parametric model of proportional hazard is appropriate to study continues variables that may likely influence the longevity. Interpretation of Cox empirical model is simpler than the parametric ones [1, 10]. Table 1 compares advantages and disadvantages of parametric, semi-parametric and nonparametric models.

Table 1. *Comparison of survival analysis approaches.*

No	Approach	Advantages	Disadvantages
1	Non parametric	Allows researchers to analyze data without knowledge of relationship between response and explanatory variables. There is flexibility of incorporating the effect of time dependent auxiliary variables.	Considers the occurrence of events during the period of time. Differences of survival times in these intervals are ignored and hence some information is lost. There is less capability of identifying significant effects of multivariable cases simultaneously compared with other models.
2	Semi parametric	There is no specified assumption on failure time distribution. Includes the capability of using ignored data. It is not dependent on the type of data distribution. Besides event occurrence, considers the occurrence time. It is supported by most statistical software.	Includes the assumption of proportional hazards over time; however, for real cases it is not true always.
3	Parametric	In the case that the distribution of parameters is known, a better analysis is performed compared to a semi parametric method. Maximum likelihood method is usually used for estimation of unknown parameters. This estimation method and its interpretation are familiar for researchers. The response is better in the case of existing left censored data and interval censored data.	It is required that the probability density function should be determined before estimating a survival function. It is not capable of considering deleted data. In the case of right censored data, its response is not essentially better compared to other approaches.

Literature indicates that semi-parametric models especially Cox proportional hazard are preferred in survival analysis by most researchers [4, 14]. Hence, many studies such as Balabram et al. [15], Abadi et al. [16], Fallahzadeh et al. [17], Baulies et al. [18], Cetin et al. [19], Rezaianzadeh et al. [20], Atashgar et al. [21], and Atashgar et al. [22] used Cox proportional hazard for analyzing patients' survival. Obviously, it is not expected that the introduced approaches provide a same efficiency on the studied clinical data. In the research of survival analysis it is important that the capabilities of different approaches are addressed. A comparative study of semi-parametric and different parametric models is not addressed by literature. This study investigates comparatively the efficiency and the capability of 1) Cox proportional hazard semi-parametric, and 2) different parametric methods (i.e. exponential, Weibull, logistic, log-normal, and Gompertz). This study also finally proposes the best empirical model for an effective survival analysis as well as the best parametric model.

This paper is structured as follows: The next section is allocated to represent the six proposed model of this paper. Section 3 provides the analysis of the proposed models of this research. In this section the superior model for a survival analysis of the breast cancer patient is introduced. Finally, the last section is allocated for remarks and conclusions.

2. Providing Proposed Models

In this research 2010 breast cancer patients who referred to three therapeutic hospital centers in Tehran (Capital of Iran) in the interval years of 2007- 2016, were investigated completely. In this extensive study, considering ethical issues, variables of 1) patients age at the time of diagnosis, 2) job status, 3) history of disease, 4) family history, 5) clanship, 6) education, 7) side of breast involvement, 8) disease stage, 9) disease severity, 10) tumor size, 11) metastasis, 12) HER2, 13) involvement of blood vessels or nerves, 14) involvement of nipple or skin, 15) involvement of lymph nodes, 16) number of vacated lymph nodes, 17) number of involved lymph nodes, 18) extra capsular in lymph nodes, 19) level of picked lymph nodes, 20) guard node, 21) estrogen and progesterone receptor, 22) pathology type, 23) surgery type, 24) hormone therapy, 25) chemotherapy, 26) radiotherapy, and 27) survival status of all the patients were investigated and recorded precisely. The investigation addressed that there is the possibility of study of 1826 patients. Censored cases (in this study all of them are the right type) correspond to individuals who are alive till the completion of this research or there are no possibility of contacting them.

Multivariable analysis of the prognosis factors of this cancer type is performed by using exponential, Weibull, Gompertz, normal, log-logistic log, and Cox proportional hazard models. Furthermore the investigation of patients' survival is evaluated also using Kaplan-Meier diagram. Survival status of the patients is regarded as the final response for the proposed models of this research.

In this research, as shown in the top row of Table 2, all the 27 variables introduced before are considered using 6 different approaches. The statistical analysis of each approaches led the researchers to estimate 6 different regression types. Table 2 shows the estimated parameters of the studied regression models. Table 3 shows the 6 models mathematically. As shown in Table 2 and Table 3 the approaches address different conditions of breast cancer survival; hence providing the best approach is an important issue in survival analysis of a breast cancer patient.

For analyzing parametric model, as well as Cox model and Kaplan-Meier diagram, R and SPSS softwares are used, respectively. In this comparative analysis the use of Akaike criteria is approached. Akaike value is calculated as the following Equation 1.

$$AIC=-2\ln(L)+2(P+K) \quad (1)$$

where P denotes the number of parameters; K is a constant coefficient (it is assumed 1 for the case that exponential and Gompertz are considered, and it is equal to 2 for Weibull, normal, and logistic cases). In Equation 1, L indicates the maximum value of the likelihood function for the model. . Akaike information criteria (AIC) addresses the fitness capability of an estimated model. The lower value of an AIC addresses the better fitness of a model.

Table 2. *Parametric Regression & Cox models Fitted to Breast Cancer Data.*

EXPONENTIAL			GOMPERTZ			WEIBULL				
P.V	SE	β	P.V	SE	β	P.V	SE	β		
0	0.014	-0.051	0	0.013	0.049	0	0.009	-0.035	Age	
0.233	1.112	1.328	-	-	-	0.231	0.72	0.862	Employee	Job
0.688	0.493	0.198	-	-	-	0.640	0.327	0.153	Teacher	
0.39	0.404	-0.347	0.91	0.409	-0.046	0.475	0.264	-0.189	Familial History	
0.008	0.316	-0.839	0	0.33	1.150	0.002	0.208	0.639	Medical History	
0.433	0.327	-0.256	0.368	0.332	0.298	0.395	0.211	-0.18	Turkish	Ethnic
0.712	0.497	0.183	0.553	0.493	-0.292	0.697	0.319	0.124	Other	
0.555	0.274	0.161	-	-	-	0.529	0.180	0.113	Left	Breast
0.115	1.13	-1.783	-	-	-	0.171	0.749	-1.026	Both	Site
0.494	0.336	0.229	0.342	0.339	-0.322	0.454	0.219	0.164	Diplom -	Education
0.143	0.523	-0.768	0.444	0.425	0.325	0.117	0.35	-0.548	Diplom	
0.166	0.061	-0.084	0.194	0.063	0.081	0.253	0.041	-0.046	Tumor Size	
0.826	0.473	-0.104	0.478	0.47	0.333	0.798	0.35	-0.078	II	
0.732	0.652	-0.223	0.622	0.653	0.321	0.755	0.429	-0.133	III	Stage
0.821	0.726	-0.164	0.819	0.721	0.165	0.737	0.467	-0.157	IV	
0.771	0.82	0.239	0.754	0.807	-0.252	0.83	0.535	0.115	II	Grade
0.869	0.816	-0.135	0.540	0.782	0.478	0.796	0.531	-0.137	III	
0.288	0.272	0.296	0.302	0.282	-0.291	0.323	0.185	0.183	HER2 receptor +	
0.988	0.339	-0.005	0.376	0.338	0.132	0.896	0.219	0.028	Vascular	Vascular-
0.717	0.391	-0.141	0.696	0.388	0.343	0.579	0.254	-0.141	Perineural	perineural
0.769	0.379	0.111	0.663	0.373	0.162	0.713	0.248	0.091	Both	Involvement
0.146	0.375	-0.546	0.089	0.374	0.636	0.067	0.243	-0.445	Extracapsular Extension	
0.207	0.379	-0.478	0.174	0.382	0.518	0.164	0.242	-0.338	Lymph Node Involvement	
0.567	0.026	0.015	0.958	0.026	0.001-	0.752	0.017	-0.005	No. Lymph Node	
0.492	0.281	-0.193	-	-	-	0.498	0.187	-0.127	Invasive	Pathology
-	-	-	0.828	0.285	-0.061	-	-	-	Insitu- Invasive	
-	-	-	-	-	-	-	-	-	Radical Mastectomy	
0.220	0.566	0.693	0.256	0.554	-0.629	0.186	0.365	0.483	partial Mastectomy	Surgery
0.023	0.459	1.039	0.019	0.462	-1.080	0.014	0.301	0.742	BCS	
0.017	0.621	-1.475	0.006	0.611	1.660	0.015	0.404	-0.981	Metastasis	
0.571	0.284	-0.161	0.885	0.275	0.039	0.697	0.184	-0.072	No. Metastasis	
0.001	0.286	0.926	-	-	-	0.000	0.192	0.680	Hormonotherapy	
0.728	1.05	-0.365	-	-	-	0.791	0.678	-0.180	Radiotherapy	
917.4			901.8			900.8			AIC	

Table 2. *Continued.*

LOG NORMAL			LOG LOGISTIC			COX				
P.V	SE	β	P.V	SE	β	P.V	SE	β		
0.000	0.009	-0.034	0	0.009	-0.036	0.000	0.015	0.066	Age	
0.239	0.844	0.993	0.174	0.713	0.969	0.396	1.145	-0.973	Employee	Job
0.881	0.340	0.051	0.726	0.315	0.11	0.994	0.55	0.004	Teacher	
0.692	0.274	-0.108	0.423	0.259	-0.207	0.203	0.418	0.532	Familial History	
0.013	0.215	0.532	0.002	0.211	0.642	0.001	0.353	-1.219	Medical History	
0.235	0.239	-0.284	0.245	0.24	-0.279	0.490	0.350	0.242	Turkish	Ethnic

LOG NORMAL			LOG LOGISTIC			COX				
P.V	SE	β	P.V	SE	β	P.V	SE	β		
0.751	0.337	0.107	0.811	0.332	0.077	0.581	0.515	-0.281	Other	
0.108	0.191	0.307	0.233	0.183	0.219	0.528	0.292	-0.184	Left	Breast
0.007	0.72	-1.919	0.121	0.867	-1.345	0.167	1.176	1.624	Both	Site
0.114	0.23	0.364	0.26	0.221	0.249	0.421	0.35	0.282	Diplom -	Education
0.549	0.364	-0.218	0.208	0.336	-0.423	0.099	0.581	0.957	Diplom	
0.241	0.051	-0.060	0.167	0.048	-0.066	0.373	0.07	0.063	Tumor Size	
0.733	0.294	0.100	0.94	0.298	0.022	0.987	0.696	-0.011	II	
0.708	0.430	0.160	0.844	0.426	0.083	0.946	0.764	-0.052	III	Stage
0.574	0.568	-0.320	0.559	0.495	-0.289	-	-	-	IV	
0.274	0.473	0.518	0.686	0.524	0.212	0.819	0.839	0.192	II	Grade
0.682	0.474	0.194	0.974	0.528	-0.017	-	-	-	III	
0.217	0.194	0.240	0.710	0.192	0.071	0.237	0.295	-0.348	HER2 receptor +	
0.969	0.240	0.009	0.780	0.228	-0.063	0.855	0.350	-0.064	Vascular	Vascular-
0.977	0.285	-0.008	0.830	0.278	-0.059	0.462	0.428	0.315	Perineural	perineural
0.520	0.273	0.175	0.628	0.255	0.123	0.827	0.399	-0.087	Both	Involvement
0.470	0.308	-0.222	0.416	0.269	-0.218	0.037	0.402	0.839	Extracapsular Extension	
0.186	0.249	-0.330	0.270	0.245	-0.271	0.596	0.410	0.217	Lymph Node Involvement	
0.304	0.018	-0.019	0.245	0.018	-0.02	0.011	0.045	0.115	No. Lymph Node	
0.594	0.198	-0.106	0.994	0.191	0.001	0.545	0.306	-0.186	Invasive	Pathology
-	-	-	-	-	-				Insitu- Invasive	
-	-	-	-	-	-	0.099	0.589	-0.972	Radical Mastectomy	
0.07	0.434	0.787	0.082	0.375	0.652	-	-	-	partial Mastectomy	Surgery
0.02	0.269	0.625	0.019	0.287	0.673	0.847	0.716	-0.138	BCS	
0.119	0.531	-0.828	0.061	0.458	-0.857	0.046	0.6522	1.299	Metastasis	
0.531	0.258	-0.161	0.558	0.239	-0.14	0.358	0.303	0.287	No. Metastasis	
0	0.207	0.802	0.000	0.203	0.762	0.059	1.272	2.398	Hormonotherapy	
0.715	0.699	-0.255	0.910	0.637	-0.071	0.888	1.043	0.147	Radiotherapy	
898.8			896.6			773.85			AIC	

Table 3. *Semi-parametric and paramedic survival models.*

	Model
COX	$h(t\|X) = h_{.}(t)$.exp (0.06 Age + 1.21 History Disease + Education (0.95 Diplom) + 0.83 EXcapsular + 0.11 No. Lymph Node + Surgery (0.97 Mastectomy) + 1.29 Metastasis + 2.39 Hormonotherapy)
LOG LOGISTIC	Logit (X) = exp (α + 0.03 Age + 0.64 History Disease + Surgery (0.65 partial Mastectomy + 0.67 BCS) + 0.85 Metastasis + 0.76 Hormonotherapy)
LOG NORMAL	$h(t\|X) = h_{.}(t)$.exp (0.03 Age + 0.53 History Disease + Breast (1.91 Both) + Surgery (0.78 partial Mastectomy + 0.62 BCS) + 0.80 Hormonotherapy)
WEIBULL	$h(t) = \alpha t^{\alpha-1}$(0.03 Age + 0.63 History Disease + + 0.44 EXcapsular + Surgery (0.74 BCS) + 0.98 Metastasis + 0.68 Hormonotherapy)
GOMPERTZ	$h(t\|X) = \alpha$.exp (0.04 Age + 1.15 History Disease + + 0.63 EXcapsular + Surgery (1.08 BCS) + 1.66 Metastasis)
EXPONENTIAL	$h(t\|X) =$A.exp (0.05 Age + 0.83 History Disease + Surgery (1.03 BCS) + 1.47 Metastasis + 0.92 Hormonotherapy)

3. Analyzing and Results

In this research 27 variables mentioned in the previous section are analyzed using statistical methods. Stepwise approach is the most widely used for variable selection technique. In this research stepwise technique is approached to provide the proposed models. The results of fitting analysis and the coefficients of the variables corresponding to each approaches are shown in Table 2.

Table 2 shows:

Older breast cancer patients (at the time that the disease is diagnosed) are less likely to survive.

Patients with chronic diseases (i.e. diabetes, blood pressure …) are less likely to survive.

Although normal and log-logistic models follow the same pattern, log-logistic has the most efficiency compared to other parametric models in Akaike term.

Akaike value of Cox model is addressed by 733.85. This AIC indicates that Cox is the most superior compared to all the parametric models.

Table 3 provides six fitted model equations of 1822 patients to analyze survival of breast cancer patients. As shown in table 3:

Cox model consists of the following significant factors : a) age (at the time that the disease is diagnosed), b) disease history, c) education, d) extra capsular extension in lymph nodes, e) number of involved lymph nodes, f) type of radical mastectomy surgery, g) metastasis, and h) hormone therapy.

The following factors are in all the parametric models: a) age (at the time that the disease is diagnosed), b) disease history, and c) surgery type.

Proportions hazard of effective factors in the estimated parametric models are approximately the same.

None of the models addresses significant impact of the following factors: a) job status, b) family history, c) clanship, d) tumor size, e) disease stage, f) degree of malignancy, g) Her2 receptor, h) blood vessels and nerve involvement, i) pathology type, j) frequency of metastasis, and k) radiotherapy.

Table 4. *Difference of deviation of the proposed models.*

	COX	LOG LOGISTIC	LOG NORMAL	WEIBULL	GOMPERTZ	EXPONENTIAL
COX	0	122.75	124.95	126.95	127.95	143.55
LOG LOGISTIC	-122.75	0	2.2	4.2	5.2	20.8
LOG NORMAL	-124.95	-2.2	0	2	3	18.6
WEIBULL	-126.95	-4.2	-2	0	1	16.6
GOMPERTZ	-127.95	-5.2	-3	-1	0	15.6
EXPONENTIAL	-143.55	-20.8	-18.6	-16.6	-15.6	0

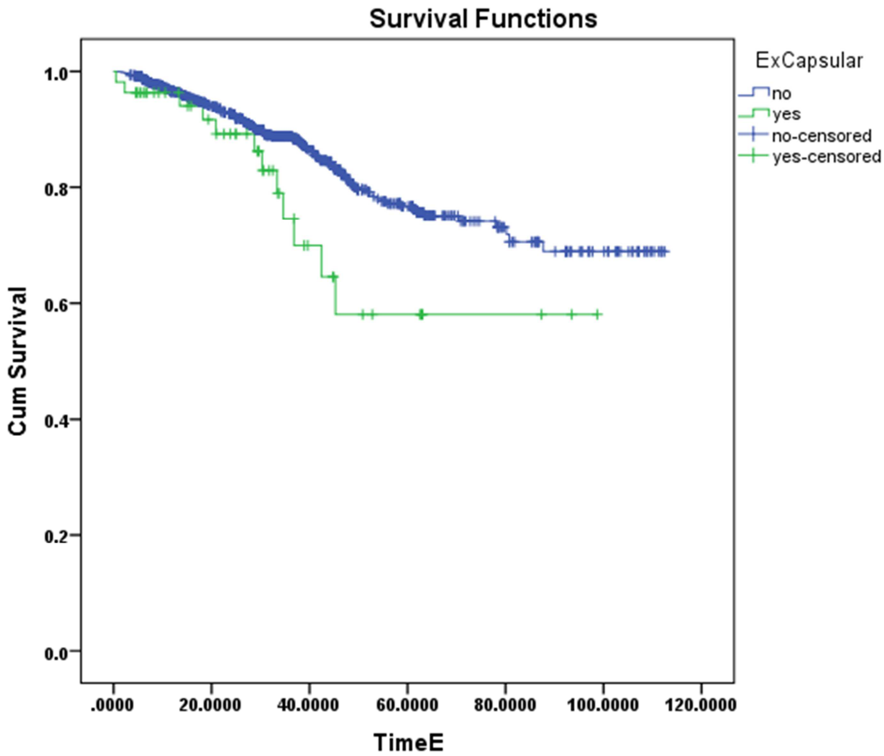

Figure 1. *The Survival curve considering Extra capsular extension.*

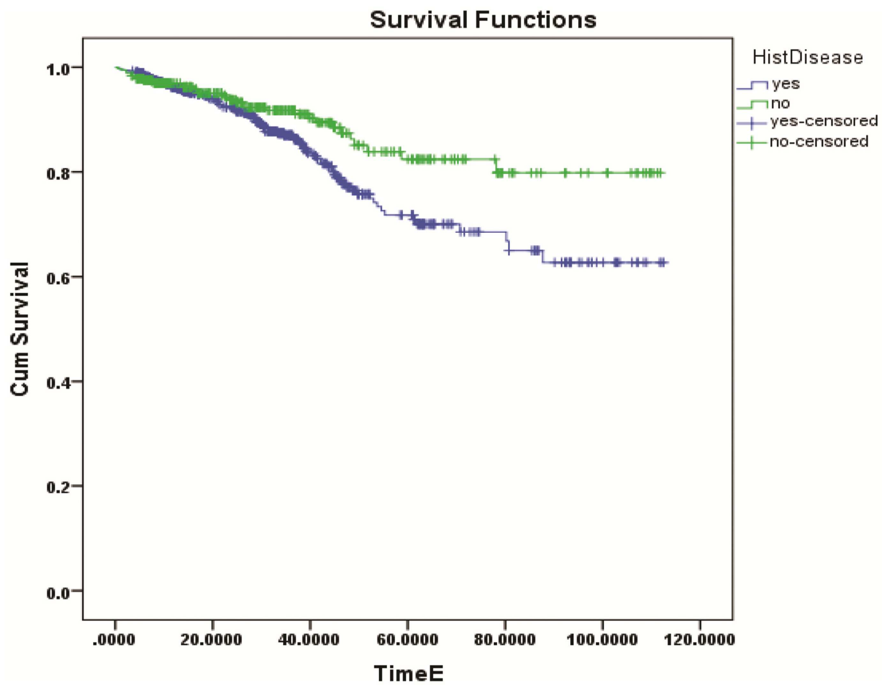

Figure 2. *The Survival curve considering medical history.*

Table 4 shows the difference of Akaike criteria between the proposed models of this study. As shown in Table 4, the differences of Akaike value of all parametric models with Cox model are very high.

In the proposed Cox model of this paper, two factors including 1) chronic disease history (such as diabetes, blood pressure and internal glands disorders such as hypo- and hyperthyroidism) (P=0.001), and 2) extra capsular extension in lymph nodes (P<0.05) are manifested significantly. However, these two factors have not been addressed by other proposed models of literature. Kaplan-Meier diagrams (shown in figures 1 and 2) illustrate graphically remarkable effects of these two variables on breast cancer patients' survival, respectively. Both of these diagrams show that extra capsular extension in lymph nodes and history of chronic diseases, affect significantly on a patient's longevity, after two years.

4. Conclusions

Literature indicates that survival analysis of breast cancer patients has been contributed by different researchers approaching parametric and semi-parametric models. These proposed models provided the opportunity for specialists to analyze the most important factors that effect on survival of patients with breast cancer.

In this extensive study considering 1822 breast cancer patients in Tehran (Capital of Iran), six different proposed models were introduced using two parametric and semi-parametric approaches. In the analyzing step, the proposed parametric and semi-parametric models were compared based on the independent parameters and Akaik criterion. This comprehensive research indicated that two proposed significant factors including 1) disease history, and 2) extra capsular extension, should be considered for a cancer breast survival analysis. It should be stated that the proposed models of the literature do not propose the two new factors for a survival consideration. The Kaplan-Meier diagram addressed that these factors are effective from the second year onwards. Furthermore, this research showed that among the parametric models, log-logistic provides the best fitted on data. However, Cox semi parametric is the most superior compared to other considered models. Since in real research cases, censored and incomplete data are used by researchers, Cox superior model by analysis of survival of prognosis variables in a clinical study, provides the capability of performing the survival analysis effectively for physicians.

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