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Lung Cancer Survival Analysis: A Comparative Evaluation of Cox Proportional Hazards and Accelerated Failure Time Models: An Analytical Study

Akciğer Kanseri Sağkalım Analizi: Cox Orantılı Tehlikeler ve Hızlandırılmış Başarısızlık Süresi Modellerinin Karşılaştırmalı Değerlendirmesi: Analitik Çalışma

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ABSTRACT Objective: This study aims to evaluate and compare the Cox Proportional Hazards (PH) model and Accelerated Failure Time (AFT) models in the survival analysis of lung cancer patients. The analysis focuses on survival times across different cell types, prior therapies, and treatment groups. **Material and Methods:** The study was conducted using a dataset containing survival times, censoring indicators, and variables such as cell type, prior therapy, and treatment group. The Cox PH model and 3 AFT models (Weibull, Log-Normal, Log-Logistic) were applied. While the Cox PH model does not assume a specific distribution for survival times, AFT models assume parametric distributions. Model performance was evaluated using the Akaike Information Criterion (AIC). **Results:** The Smallcell type was identified as the most aggressive cancer type, with the lowest survival probability. AFT models, particularly the Weibull AFT model, provided a better fit to the data than the Cox PH model, as indicated by lower AIC values. Prior therapy was associated with lower survival probabilities, suggesting higher risk among these patients. The standard treatment group showed slightly better survival over time. **Conclusion:** This study highlights the importance of selecting an appropriate survival analysis model based on the characteristics of lung cancer data. While the Cox PH model offers flexibility, the Weibull AFT model provided better insights and fit. These findings emphasize the critical role of model selection in accurately understanding and predicting patient outcomes in lung cancer survival analysis.

Keywords: Lung cancer; survival analysis; Cox proportional hazards model; accelerated failure time model

ÖZET Amaç: Bu çalışma, akciğer kanseri hastalarının sağkalım analizinde Cox Orantılı Tehlikeler [Proportional Hazards (PH)] modeli ile Hızlandırılmış Başarısızlık Süresi [Accelerated Failure Time (AFT)] modellerini değerlendirmeyi ve karşılaştırmayı amaçlamaktadır. Farklı hücre tipleri, önceki tedavi ve tedavi grupları arasındaki sağkalım süreleri incelenmiştir. **Gereç ve Yöntemler:** Analiz, sağkalım süreleri, sansür göstergeleri ve hücre tipi, önceki tedavi ve tedavi grubu gibi değişkenleri içeren bir veri seti ile gerçekleştirilmiştir. Veri setine Cox PH modeli ve 3 AFT modeli (Weibull, Log-Normal, Log-Lojistik) uygulanmıştır. Cox PH modeli, belirli bir dağılım varsaymazken, AFT modelleri parametrik dağılımlar varsayar. Model performansı Akaike Bilgi Kriteri [Akaike Information Criterion (AIC)] ile değerlendirilmiştir. **Bulgular:** Küçük hücre tipi en düşük sağkalım olasılığı ile daha agresif bir kanser tipi olarak belirlenmiştir. AFT modelleri, özellikle Weibull AFT modeli, daha düşük AIC değerleri ile Cox PH modeline kıyasla daha iyi uyum sağlamıştır. Önceki tedavi, daha düşük sağkalım olasılıkları ile ilişkili bulunmuş, bu da daha yüksek risk altında olduklarını göstermiştir. Standart tedavi grubu ise zamanla biraz daha iyi performans göstermiştir. **Sonuç:** Çalışma, akciğer kanseri verilerinin özelliklerine uygun sağkalım analiz modelinin seçilmesinin önemini vurgulamaktadır. Cox PH modeli esneklik sunarken, özellikle Weibull AFT modeli, daha iyi içgörüler ve uyum sağlamıştır. Bu bulgular, model seçiminin hasta sonuçlarını doğru anlamak ve tahmin etmek açısından önemini ortaya koymaktadır.

Anahtar Kelimeler: Akciğer kanseri; sağkalım analizi; Cox orantılı tehlikeler modeli; hızlandırılmış başarısızlık süresi modeli

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Survival analysis is a critical component of medical research and enables the evaluation of time-to-event data such as patient survival times. Among the statistical models used in survival analysis, the Cox Proportional Hazards (PH) model and the Accelerated Time to Failure (AFT) model are 2 of the most prominent approaches. Each model offers different advantages and addresses different aspects of survival data, making the choice between them dependent on the research context and underlying data characteristics. The Cox PH model, introduced by Cox, has become a cornerstone of survival analysis due to its semiparametric structure that does not assume a specific distribution for survival times.[1] By estimating the hazard ratio, the model provides insights into the relative risk associated with covariates while adjusting for other variables in the model. Its flexibility and interpretability have led to its widespread adoption in clinical trials.[1,2] In contrast, the AFT model, which includes parametric models such as the Weibull, Log-Normal, and Log-Logistic distributions, offers an alternative by directly modeling survival time. The AFT model assumes that covariates accelerate or slow down survival by a fixed factor, which may be particularly useful when the proportional hazards assumption is violated.[3,4] The parametric nature of the AFT model allows for more precise estimates of survival times, which may be advantageous in certain clinical settings where the distribution of survival times is well understood. The choice between these models can have important implications for the conclusions drawn from survival data. While the Cox PH model is generally preferred for its robustness and flexibility, the AFT model offers valuable insights, particularly when the proportional hazards assumption does not hold.[5-7] In clinical trials, where patient outcomes are often a primary concern, the ability to accurately model survival times and understand the effects of covariates on these times is crucial.[8,9] Given the importance of these models in survival analysis, this study aims to compare the Cox PH and AFT models using real-world lung cancer survival data. By applying both models to the same dataset, this research aims to highlight the strengths and weaknesses of each approach and to provide researchers with guidance in selecting the appropriate model for their study.

MATERIAL AND METHODS

The data used in this study are from the Veterans Administration Lung Cancer Trial reported by Prentice. This randomized clinical trial was designed to evaluate a test chemotherapy treatment.[3,10] Since the study contains publicly available data, it does not require ethics committee approval. Data Preprocessing Initially, the data were preprocessed to prepare for survival analysis. The Python programming language, specifically the pandas library, was used for data preprocessing.[11] Statistical models 3 different AFT models were used to compare the Cox PH and AFT models: Weibull, Log-Normal, and Log-Logistic. These models were selected because of their widespread use in survival analysis and their ability to model time-to-event data under different assumptions.

SEMIPARAMETRIC: COX PROPORTIONAL HAZARDS MODEL

The Cox model estimates the hazard function, which allows the inclusion of covariates to determine their effects on survival without assuming a specific distribution for survival times, as follows: where $h_0(t)$, is called the baseline hazard rate.[12] This semiparametric model was implemented using the lifelines library in Python.[13,14]

$$h(t\backslash x) = h_0(t)exp\sum_{i=1}^{m} h_i(x_i - \bar{x}_i) \quad (1)$$

PARAMETRIC MODEL: ACCELERATED FAILURE TIME MODEL

In parametric regression models, the distribution of survival time is known and the probability density, hazard, and survival functions are precisely defined. By defining these functions, the parameter estimate is made by obtaining information about all data of the estimated survival curve. The conditional hazard function, which is a function of the independent variables, is used to model the independent variables affecting the survival time with parametric regression. The conditional hazard function is as follows. Here, β is the regression coefficient vector, and $h_0(t)$ is any unspecified basic hazard function of T.[6]

$$h(t\backslash x) = h_0(t)exp(x\beta) \quad (2)$$

When determining the conditional hazard function for the PR model, the basic hazard function of the distribution that the survival time is suitable for should be used. The most commonly used models are based on distributions such as Weibull and log-normal. In this article, Weibull, Log-Normal, and Log-Logistic models are used, The Weibull AFT model was implemented using WeibullAFTFitter from the lifelines library.[6,15] This parametric model assumes that survival times follow a Weibull distribution and provides estimates of the acceleration factor that show how covariates affect survival times.[16] The Log-Normal AFT model assumes that the logarithm of survival times follows a normal distribution. This model was fit using LogNormalAFTFitter from the lifelines library, which provides insights into survival times under the assumption of log-normality.[5] Another parametric model, the Log-Logistic AFT model, assumes that survival times follow a log-logistic distribution. This model was fit using LogLogisticAFTFitter from the lifelines library and is particularly useful when the hazard function exhibits a non-monotonic pattern.[8] Each model was fitted to the lung cancer dataset using the specified survival time and censoring variables. The Lifelines library was used for model fitting and summary generation. The performance of each model was evaluated based on the Akaike Information Criterion (AIC) values. These metrics provide a comparative understanding of model fit and predictive accuracy. AIC is used to evaluate the relative quality of statistical models for a given dataset. Lower AIC values indicate a better fit by balancing model complexity and goodness of fit.[17] AIC is calculated as follows.

$$AIC = -2logL + 2k \qquad (3)$$

All analyses were performed using Python 3.10 with the lifelines library (developed by Cameron Davidson-Pilon, Canada) for survival analysis and matplotlib (developed by John D. Hunter, United States) for plotting model coefficients.

NONPARAMETRIC MODEL: KAPLAN-MEIER

The Kaplan-Meier method is a non-parametric method used to perform survival analysis. In this method, the survival function S(t), is calculated as the cumulative product of the times during which the event (e.g. death, disease progression) does not occur. The Kaplan-Meier survival estimator is expressed as follows. Here, t_i represents each time point at which the event occurs. d_i, is the number of individuals experiencing the event at time t_i.n_i, is the number of individuals surviving at time t_i (those who have not yet experienced the event and are still under observation).

$$S(t) = \prod_{t_i<t} \left(1 - \frac{d_i}{n_i}\right)$$

In this study, the Kaplan-Meier method was used to analyze survival probabilities based on different cell types (Adeno, Large, Smallcell, Squamous), prior therapy status, and treatment groups. The Kaplan-Meier analysis updates the survival function whenever an event occurs, allowing the visualization of time-dependent changes in survival probabilities for each group. The Kaplan-Meier method was implemented using the lifelines library in the Python programming language.[18,19]

RESULTS

Figure 1 shows the distribution of survival times. Time is on the X-axis and the frequency of individuals with this time is on the Y-axis. The graph shows that survival times are distributed over a wide range, but it is understood that more individuals survive in certain periods. The density of individuals with survival times between 5 and 10 time units is particu-

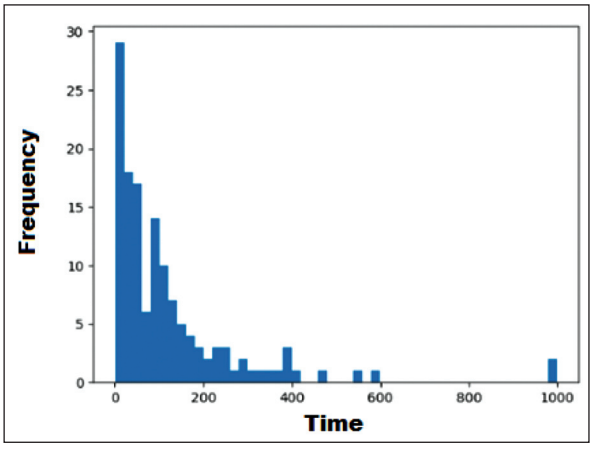


FIGURE 1: Distribution of survival times.

larly striking. Such a distribution indicates that survival rates are higher in a certain period, but that there is a heterogeneous distribution in general. It can also be observed that the number of individuals decreases as the survival time increases. This indicates that the probability of survival decreases over time, which is a typical survival analysis result.

Table 1 compares the AIC values across different survival analysis models, including the Cox proportional hazards model and the three accelerated failure time models, Weibull, Log-Normal, and Log-Logistic. The Cox model shows an AIC value of 25.84, which is the baseline value for comparison with AFT models. The Weibull model has an AIC value of 157.19 when applied as a general model. However, when applied as an AFT model, the AIC improves significantly to 10.45, indicating a better fit under the AFT framework compared to its general form and the Cox model. The AIC value of the Log-Normal model as a general model is 154.53, and drops to 17.09 in the AFT context. This shows that the Log-Normal AFT model fits the data better than its general counterpart and provides a good alternative to the Weibull AFT model, but is not as effective. The overall AIC value for the Log-Logistic model is 156.38, while the AFT application reduces the AIC to 15.60. This model also shows an improved fit as the AFT model but still lags slightly behind the Weibull AFT model. It reveals that the AFT models, especially the Weibull AFT model, provide a significantly better fit to the data compared to the Cox Proportional Hazards model, as evidenced by the lower AIC values. The table highlights the importance of choosing the appropriate model framework for survival analysis; AFT models, especially the Weibull, show superior performance for this data set.

TABLE 1: Comparison of AIC values for Cox proportional hazards and AFT models.

Models	AIC value for fitter	AIC value for AFT fitter
Cox PH Model	25.84	-
Weibull	157.19	10.45
Log-Normal	154.53	17.09
Log-Logistic	156.38	15.60

AIC: Akaike information criterion; AFT: Accelerated failure time; PH: Proportional Hazards.

Figure 2 shows the differences in survival times of different cell types, prior therapy, and treatment groups based on Kaplan-Meier survival analysis. The lines represent the estimated survival probabilities, and the shaded areas around each line represent the 95% confidence intervals for these estimates. For example, the green line and shaded area represent the survival probabilities and confidence intervals for the Adeno cell type. These shaded areas help visualize the uncertainties in the survival estimates, with wider intervals indicating greater uncertainty in the survival probability estimates. For cell types, the Smallcell type has a noticeably lower survival probability compared to other cell types, suggesting that it may be a more aggressive form of cancer.

Survival based on the prior therapy variable shows the difference in survival between groups that have received prior therapy and those that have not. Patients who received prior therapy appear to have a lower probability of survival compared to those who did not, indicating that the effect of prior treatments may be limited or negative.

Additionally, the survival analysis of different treatment groups reveals that while the survival probabilities for the standard and test groups are similar initially, the survival rate for the test group decreases slightly over time, potentially reflecting differences in the effectiveness of the treatments over longer periods.

In Figure 3, according to the Weibull model, the "Treatment=2" (possibly the new treatment being tested) group shows a lower survival probability compared to the "Treatment=1" (standard treatment) group. This may indicate that the new treatment may be less effective at the beginning or carry a higher risk. The log-logistic model shows a similar trend. The "Treatment=2" group shows a faster decrease in survival probability over time. This may suggest that the effect of the new treatment provides less benefit after a certain period. In the log-normal model, the "Treatment=2" group shows a lower survival probability compared to the "Treatment=1" group. All three models show a similar trend, emphasizing that the new treatment leads to a lower survival probability. In the Cox model, the survival functions of the

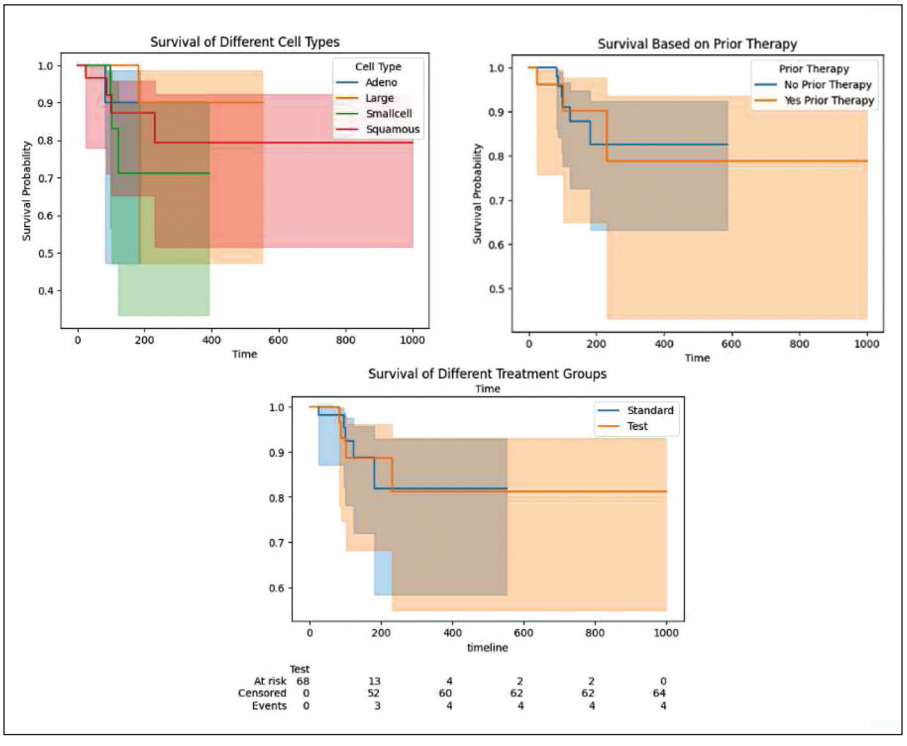


FIGURE 2: Kaplan-Meier survival analysis by cell type, prior therapy, and treatment groups.

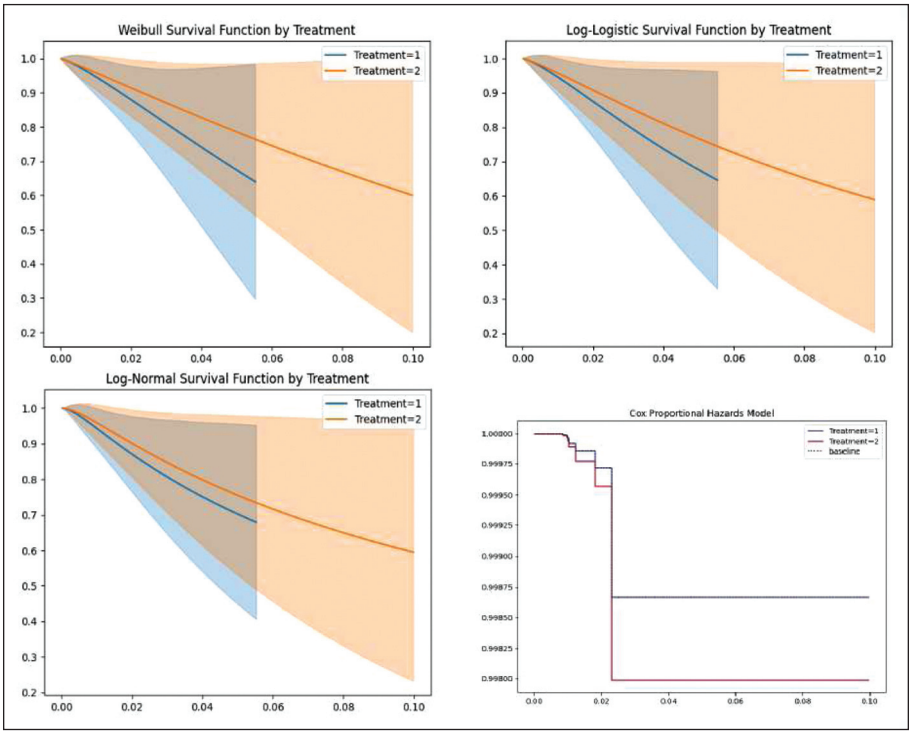


FIGURE 3: Survival analysis by treatment groups using various statistical models.
1: Standard; 2: Test.

"Treatment=1" and "Treatment=2" groups are quite close to each other. This may indicate that the Cox model does not detect a significant difference between the treatment groups. However, when the

trends in the Cox model are taken into account, it can be observed that the treatment differences lose their effect over time.

In Figure 4, according to the Weibull model, significant differences are observed between the survival probabilities of different cell types. In particular, the group with "Celltype=4" (Squamous) shows a lower survival probability compared to other cell types. This may suggest that the Squamous cell type may have a more aggressive progression. The log-normal model also shows a similar trend, but it is observed that the group with "Celltype=2" (large) exhibits a better survival probability over time. This model emphasizes that some cell types have similar survival probabilities at the beginning, but the differences become more pronounced over time. The log-logistic model reveals the differentiation of survival probabilities over time more clearly. Again, the group with "Celltype=4" (Squamous) has the lowest survival probability. There are also significant differences between other cell types. Although the survival differences between cell types are less pronounced in the Cox model, it can be observed that the "Celltype=4" group is generally at risk. While the survival functions of the model are generally similar, it may be understood that certain cell types (especially Squamous) are at higher risk.

In Figure 5, according to the log-normal model, the survival probability of the group that received prior therapy (Prior Therapy=2) decreases significantly over time. The group that did not benefit from therapy (Prior Therapy=1) has a higher survival rate. This situation shows that patients who received prior therapy are at higher risk over time. The log-logistic model also shows a similar trend. The group that received prior therapy exhibits a lower survival probability over time. The survival rate of the group without therapy is more stable. This model emphasizes that the group that received therapy is at a higher risk in terms of survival, especially in the long

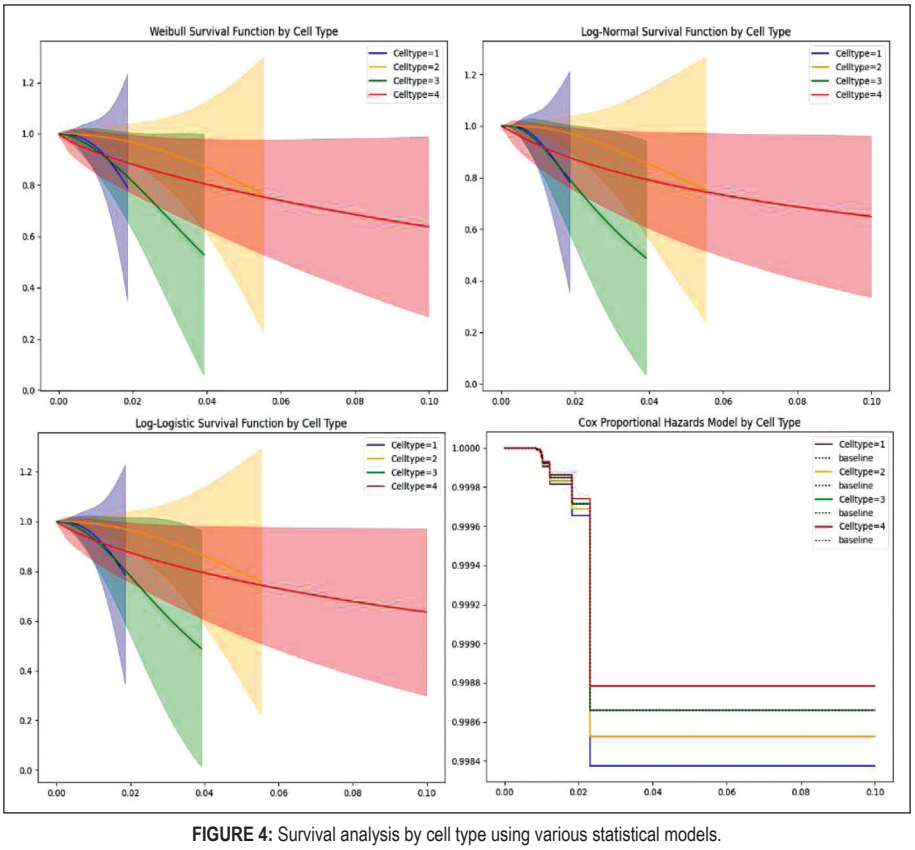
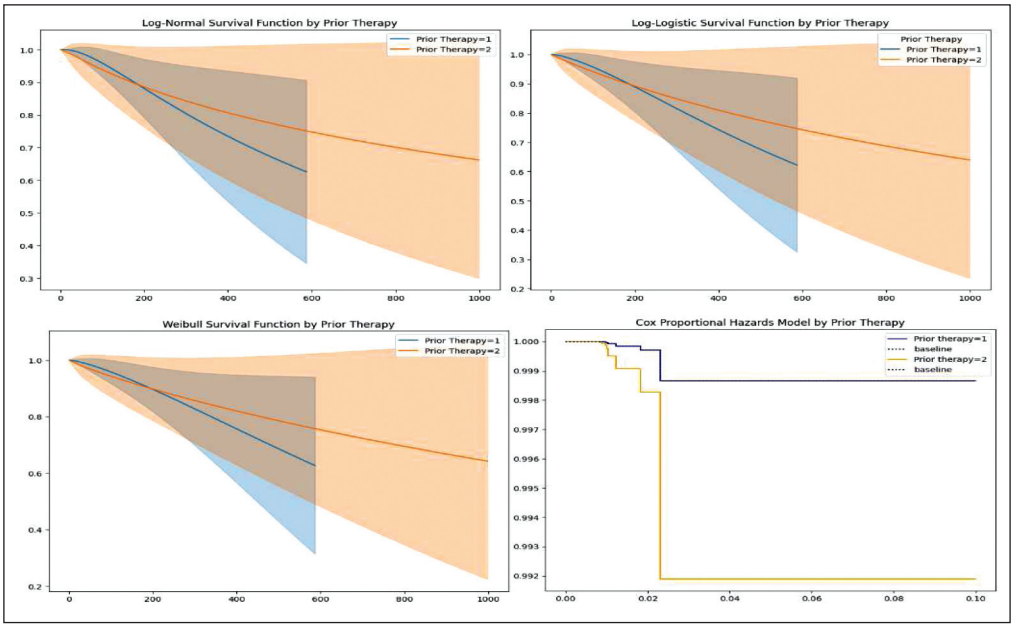


FIGURE 4: Survival analysis by cell type using various statistical models.
Adeno: 1; Large: 2; Smallcell: 3; Squamous: 4



FIGUREL 5: Survival analysis by prior therapy using various statistical models.
1: No; 2: Yes.

term. Similar results are observed in the Weibull model. Patients who received prior therapy have lower survival rates over time, suggesting that this group may have a worse prognosis over time. In the Cox model, the difference between the 2 groups becomes more pronounced. The group that received prior therapy (orange line) has a higher risk profile, while the group without therapy (blue line) has a lower risk. The Cox model reveals statistically significant differences in risk between these two groups.

DISCUSSION

In this study, survival analysis was performed using the Cox PH model and the AFT models. It was shown that both models provide critical tools for survival analysis and provide researchers with the opportunity to model survival times in different contexts. While the Cox PH model offers flexibility thanks to its semiparametric structure, AFT models can better fit data sets by directly modeling survival times.

The Cox PH model is widely used to interpret survival data by estimating hazard ratios. However, when the basic assumption of this model, the proportional hazards assumption, is not met, the model's estimates can be misleadingi.[5] In this case, parametric models such as AFT models can provide more accurate estimates of the distribution of survival times.[7]

Among the AFT models used in this study, the Weibull model showed particularly strong performance. This model stands out with its ability to accurately predict survival times and is a preferred model in survival analysis studies.[19] On the other hand, Log-Normal and Log-Logistic models have also provided useful insights under different distributions of survival times. In particular, the fact that the Log-Logistic model can successfully capture non-monotonic patterns in survival functions makes it preferable in certain contexts.[3]

Whether AFT models are suitable for survival analysis depends on the context of the study and the characteristics of the data set. Although the Cox PH model is generally more flexible and has a wide range of uses, AFT models may provide more accurate results under certain assumptions.[8] Therefore, researchers need to consider the nature of the data set and the objectives of the study when choosing the most appropriate model for their studies.[4]

The findings of this study are in line with previous studies in the literature. For example, the study by

Bradburn et al. also showed that AFT models provide better results than the Cox PH model for certain clinical data sets. Similarly, the study by Klein and Moeschberger emphasizes that AFT models perform better, especially when parametric survival time distributions are suitable.[8,16] The results of this study reveal how important the correct selection of survival analysis models is, especially in clinical trials, to understand patient outcomes. Researchers should carefully evaluate the characteristics of the data sets they use in their studies and make the most appropriate model selection accordingly. This will contribute to obtaining more accurate estimates and results.

CONCLUSION

In this study, the Cox proportional hazards model, which is widely used in survival analysis, and accelerated failure time models were compared. While the Cox PH model offers a flexible and semiparametric approach under the proportional hazards assumption, AFT models stand out as parametric approaches that directly model survival time. The findings obtained in the study show that both models offer advantages for certain data structures and research contexts. AFT models may perform better, especially in cases where the data sets do not meet the proportional hazards assumption. Weibull, Log-Normal, and Log-Logistic AFT models were successful in modeling survival times under certain assumptions and provided a better fit compared to the Cox model with lower AIC values. However, the Cox PH model continues to be preferred by researchers because it is generally more flexible and has a wide range of uses. Our study highlights important factors to consider when selecting survival analysis models. It is of great importance for researchers to make model selections by considering the nature of the datasets, the validity of the proportional hazards assumption, and the research questions. In addition, this study shows that AFT models can provide more accurate and meaningful results, especially when the distribution of survival times is well known. In conclusion, this study reveals that the selection of survival analysis models can have a decisive effect on the results of the study. The comparison between the Cox PH model and AFT models shows that both approaches play important roles in the analysis of health data and that these models should be selected carefully and consciously. These findings can guide the design of clinical trials and the interpretation of the results.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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