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Application of a 2 Parameter Weibull Distribution in Modeling of State Holding Time in HIV/AIDS Transition Dynamics

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Abstract

This study investigates the application of the two-parameter Weibull distribution in modeling state holding times within HIV/AIDS progression dynamics. By comparing the performance of the Weibull-based Accelerated Failure Time (AFT) model, Cox Proportional Hazards model, and Survival model, we assess the effectiveness of these models in capturing survival rates across varying gender, age groups, and treatment categories. Simulated data was used to fit the models, with model identification criteria (AIC, BIC, and R^2) applied for evaluation. Results indicate that the AFT model is particularly sensitive to interaction terms, showing significant effects for older age groups (50 - 60 years) and treatment interaction, while the Cox model provides a more stable fit across all age groups. The Survival model displayed variability, with its performance diminishing when interaction terms were introduced, particularly in older age groups. Overall, while the AFT model captures the complexities of interactions in the data, the Cox model's stability suggests it may be better suited for general analyses without strong interaction effects. The findings highlight the importance of model selection in survival analysis, especially in complex disease progression scenarios like HIV/AIDS.

Keywords

Weibull Distribution, AFT Model, Cox Proportional Hazards, HIV/AIDS, State Holding Time, Survival Analysis

1. Introduction

Several previous studies on modeling HIV/AIDS infection progression relied on the Markov property, assuming that future disease states depend only on the current state and not on prior states. However, this assumption often does not hold, as the waiting time (state holding time) distributions are non-exponential and may depend on subsequent stages. This violation of the Markov property led to the introduction of semi-Markov models, which explicitly define the distribution of holding times using extensions of the exponential distribution. These models allow for a non-constant hazard rate, improving upon the constant hazard assumption inherent In Exponential Markov models.

[1] applied various survival models, including Markov models and parametric survival models such as the Exponential and Weibull distributions, to investigate the state holding times in HIV/AIDS progression. The study demonstrated that while the Exponential model is simple, its assumption of a constant hazard rate oversimplifies the varying risks that patients face as they progress through different stages of the disease. This leads to less accurate estimates of the time spent in each disease state. Moreover, the Markov model's assumption that transitions are independent of prior states further oversimplifies the complex progression of HIV/AIDS, where prior stages and treatments significantly influence future states. [1] also did not incorporate critical covariates such as gender, age, and treatment adherence, all of which play essential roles in determining state holding times. The study highlighted the need for more flexible models that account for these variables.

[2] utilized a Cox Proportional Hazards model to estimate survival times and transitions between states in HIV-infected individuals before the introduction of antiretroviral therapy (ART). The Cox model is semiparametric, allowing for the estimation of hazard ratios between subgroups without assuming a specific baseline hazard function. However, its proportional hazards assumption-which assumes that hazard ratios between subgroups remain constant over time-may not hold when risks change significantly, such as when patients progress to later stages of HIV/AIDS or initiate ART. Additionally, the model does not account for time-varying covariates, such as ART initiation, which can drastically alter state transitions and disease dynamics. This lack of time-varying covariates limits the model's applicability in long-term disease progression studies.

[3] applied a multi-state Markov model to study the mortality of HIV-1-infected patients during the first year of ART. The model considered transitions between different stages of the disease but oversimplified the progression by assuming that future states depend only on the current state, ignoring the effects of prior treatments and disease history. Furthermore, the study failed to incorporate critical covariates, such as gender and CD4 count, which are significant factors affecting disease progression. The study's reliance on the memoryless assumption of the Markov model limited its ability to accurately capture the complex progression of HIV/AIDS.

[4], the comparison between the Accelerated Failure Time (AFT) Weibull model and the Cox Proportional Hazards model in medical research highlighted significant differences between these two models in terms of assumptions and handling time-to-event data. [4] employed the AFT Weibull model to model the

survival times of cancer patients. The study emphasized the strength of the AFT Weibull model in directly estimating the effect of covariates on the median survival time, which contrasts with the Cox model, which estimates hazard ratios. The AFT Weibull model proved more flexible than the Exponential model, particularly when proportional hazards could not be assumed. However, the Cox model's semi-parametric nature—which does not require a specific form for the baseline hazard—was advantageous when proportional hazards were met. Despite this, the study did not explore time-varying covariates or interaction effects between covariates.

[5] compared the Weibull AFT and Cox Proportional Hazards models in clinical trials with breast cancer patients. The study aimed to assess the effects of treatment and various patient characteristics on survival times. The Weibull AFT model was selected for its ability to model survival data where hazard rates could increase or decrease over time, making it suitable for long-term studies. The Cox model was employed alongside the Weibull AFT model to estimate hazard ratios. However, while the Cox model is flexible and widely used due to its minimal assumptions, it may not always be as interpretable as the AFT model, which directly estimates the effect of covariates on survival time. The study recommended using both models to gain different insights, but it did not address interaction effects or time-varying covariates, leaving a gap in the analysis of complex survival data.

In [6], in their research, the application of both AFT and Cox models for survival data in medical research further emphasized the utility of the AFT Weibull model when survival times do not follow proportional hazards. The Weibull distribution within the AFT framework was favored for its flexibility in accommodating increasing or decreasing hazard rates over time, making it suitable for diseases like HIV/AIDS, where progression changes over time. However, Collett also noted that the Cox model, with its ease of interpretation and semi-parametric nature, remains the default in many survival analyses when proportional hazards are valid. Despite its usefulness, the Cox model may not offer as much detailed insight in cases where survival times deviate from proportional hazards, an area where the AFT model excels. Nevertheless, Collett did not fully address time-varying covariates or interaction effects, which are critical for understanding complex disease dynamics.

[7] applied both Weibull AFT and Cox Proportional Hazards models in the context of cardiovascular disease and mortality data. The study aimed to compare the models in their ability to predict long-term survival based on patient-level covariates. The Weibull AFT model was used to estimate how covariates such as age, gender, and treatment group affected time to event, with the ability to model both increasing and decreasing hazard rates over time. However, the study found that when the proportional hazards assumption was violated, the Weibull AFT model provided more reliable and interpretable results, while the Cox model remained the preferred tool when proportional hazards were reasonably assumed. The study did not fully explore the use of interaction terms or time-varying covariates, which

are significant in chronic diseases like HIV/AIDS.

[8] applied both the Cox and Weibull AFT models in a longitudinal study of HIV/AIDS progression, focusing on the effects of covariates such as CD4 count, viral load, and treatment type on survival times. The study highlighted the advantage of the AFT Weibull model in estimating survival time ratios for different patient characteristics, making it particularly useful for long-term progression studies. The Cox model, while flexible in estimating hazard ratios, was limited when the proportional hazards assumption did not hold. The study concluded that the AFT Weibull model was better suited for understanding the effect of covariates on survival time, especially when hazard rates were non-constant, while the Cox model was effective in handling censored data.

2. Gaps and Current Study's Approach

The limitations across these studies demonstrate a clear need for more flexible models that can account for time-varying covariates, interaction effects, and history dependent transitions. The current study addresses these gaps by employing the Weibull distribution, which allows for varying hazard rates across different stages of HIV/AIDS progression. It also includes critical covariates, such as gender, age, and treatment adherence, and examines their interaction effects on state holding times. Furthermore, this study incorporates time-varying covariates, such as changes in treatment status, which is a crucial factor in long-term HIV/AIDS management. The use of semi-Markov models improves upon the traditional Markov models' limitation of assuming memoryless transitions, providing a more detailed and accurate understanding of disease progression dynamics.

By integrating both AFT Weibull and Cox Proportional Hazards models, this study offers a robust framework for addressing the shortcomings identified in previous research. The combination of these models enables the exploration of time-varying hazards and covariates, while also providing more nuanced insights into how patient characteristics influence the progression of HIV/AIDS. This research thus fills a crucial gap in the literature by offering a more flexible, covariate-rich, and historically aware approach to modeling state holding times in HIV/AIDS progression.

3. Materials and Methods

2 Parameter Weibull distributions and their modifications, namely the accelerated failure time (AFT) and the Cox Proportional Hazard models, were used in modeling the waiting time (state holding time) in the Semi Markov models [9] [10]. The assumption and the effectiveness of their hazard functions in addressing the failure rates of specific states in the dynamic evolution of HIV/Aids are discussed. Data Simulated using R software was fitted on the models and Parameters, P-value, Z-values standard error, and AD value estimated using the same software [11].

For a two-tailed test using the Z-statistic, the P-value is calculated as:

$$P = 2 \times \left(1 - \Phi\left(|Z|\right)\right) \tag{1}$$

where: Z = calculated Z-statistic, and $\Phi(Z)$ = cumulative distribution function (CDF) of the standard normal distribution [12].
The Z-statistic is calculated as:

$$Z = \frac{\hat{\beta}}{\mathrm{SE}\left(\hat{\beta}\right)} \tag{2}$$

where: Z = calculated Z-statistic, and $\mathrm{SE}\left(\hat{\beta}\right)$ = standard error of the estimated parameter $\hat{\beta}$.

The Z-statistic measures how many standard deviations an observed statistic is from the mean under the null hypothesis [13]. The standard error (SE) represents the accuracy of a sample statistic in approximating the population parameter, which is the standard deviation of the sample mean's distribution.

Consider an estimated parameter $\hat{\beta}$. The formula for the standard error as highlighted by [14] is given as follows:

$$\mathrm{SE}\left(\hat{\beta}\right) = \sqrt{\mathrm{Var}\left(\hat{\beta}\right)} \tag{3}$$

The Anderson-Darling test is widely used to test a given distribution's goodness-of-fit. It evaluates how well the data follow the specified Weibull distribution [15]. The test statistic is given by:

$$A^2 = -n - \frac{1}{n}\sum_{i=1}^{n}\left((2i-1)\left[\log F\left(x_i\right) + \log\left(1 - F\left(x_{n+1-i}\right)\right)\right]\right) \tag{4}$$

3.1. Model Selection Criteria

We used model identification criteria such as the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and log-likelihood to assess and compare the performance of each model. AIC and BIC provide a trade-off between model complexity and goodness-of-fit. A lower AIC/BIC value indicates a better-fitting model with fewer parameters [16].

AIC:

$$\mathrm{AIC} = -2 \times \log(L) + 2k \tag{5}$$

BIC:

$$\mathrm{BIC} = -2 \times \log(L) + k \times \log(n) \tag{6}$$

where:

- $\log(L)$ is the log-likelihood of the model,
- k is the number of parameters, and,
- n is the sample size.

3.2. Parameter Estimation

Parameter estimates for the shape and scale parameters of the Weibull distribution, as well as for covariates in the AFT and Cox models, were obtained using

MLE. These estimates are provided along with their corresponding standard errors (SE), Z-values, and P-values in **Table 2**.

3.3. Hypothesis Testing

For each estimated parameter, Z-statistics were used to test the null hypothesis that the coefficient is equal to zero (no effect).

P-values were calculated to assess the statistical significance of the model parameters. A P-value less than the chosen significance level ($\alpha = 0.05$) indicates that the corresponding parameter is statistically significant.

3.4. Anderson-Darling Test for Goodness of Fit

To assess the goodness-of-fit for the Weibull distribution, we used the Anderson-Darling (AD) test. The AD test evaluates how well the data follow the specified Weibull distribution. A Lower AD values depicts a better fit of the Weibull distribution to the data.

3.5. Result Presentation

The parameter estimates, standard errors, Z-values, P-values, and goodness-of-fit statistics (AIC, BIC, and AD value) are reported in **Table 2** for each model. Additionally, model fit statistics (AIC, BIC) were used to compare the models, with the lowest AIC and BIC indicating the best-fitting model for each gender and age group.

Akaike information criteria (AIC), Bayesian information criteria) and the log-likelihood criteria (LL) were used to compare the performance of the models in modeling the state holding time [17]-[19].

In this study, the natural logarithm (logarithm base e) was used for all logarithm functions. The significance level, $\alpha = 0.05$, was chosen as it is a commonly accepted threshold in statistical hypothesis testing, ensuring a 5% probability of rejecting a true null hypothesis."

3.6. Hazard Function

The hazard function, hazard rate, and failure rate refer to the probability of failure in an infinitesimally small time. It is the probability of surviving for an additional time δt having survived for t hours. It is a measure of risk, the greater the hazard the greater the chances of failure.

Let $r(t)$ be the hazard function for a given distribution, then:

$$\begin{aligned} r(t) &= \frac{\mathrm{P}\left(X \in (t, t+\delta t)\right)}{(X > t)} = \frac{\mathrm{P}\left(X \in (t, t+\delta t), X > t\right)}{\mathrm{P}(X > t)} \\ &= \frac{\mathrm{P}\left(X \in (t, t+\delta t)\right)}{\mathrm{P}(X > t)} = \frac{f(t)\mathrm{d}t}{1 - F(t)} = \frac{f(t)\mathrm{d}t}{S(t)} \end{aligned} \tag{7}$$

where $S(t) = 1 - F(t)$; $S(t)$ is the survival function.

3.7. Modeling of State Holding Time Using Two Parameter Weibull Distributions

The Weibull distribution has two parameters, namely λ, the shape parameter, and θ, the scale parameter. The probability density function of the Weibull distribution is given by:

$$f(x)=\begin{cases}\dfrac{\lambda x^{\lambda-1}}{\theta^{\lambda}}\exp\left[-\left(\dfrac{x}{\theta}\right)^{\lambda}\right], & \text{for } x>0,\theta>0,\lambda>0\\ 0, & \text{elsewhere}\end{cases} \tag{8}$$

The survival function is given by:

$$S(t)=\exp\left[-\left(\frac{x}{\theta}\right)^{\lambda}\right] \tag{9}$$

The hazard function is given by:

$$h(t)=\frac{f(x)}{S(t)}=\frac{\dfrac{\lambda x^{\lambda-1}}{\theta^{\lambda}}\exp\left[-\left(\dfrac{x}{\theta}\right)^{\lambda}\right]}{\exp\left[-\left(\dfrac{x}{\theta}\right)^{\lambda}\right]}=\frac{\lambda x^{\lambda-1}}{\theta^{\lambda}}=\left(\frac{\lambda}{\theta^{\lambda}}\right)x^{\lambda-1} \tag{10}$$

The hazard function depends on x. For $\lambda>1$ hazard rate will increase and for $\lambda<1$ hazard rate decreases, for $\lambda=1$ the hazard rate will be constant in a special case of exponential distribution. The hazard function, $h(t)=\left(\frac{1}{\theta}\right)$, which is a constant similar to the hazard function of the exponential distribution. Therefore, exponential distribution is a special case of Weibull distribution and can be used where exponential distribution is used as long as $\lambda=1$. Weibull distribution is therefore able to care of the varying hazard rates at varied stages of the disease progression accommodating the effect of the covariates, which indirectly or directly affects the failure rates. However, it is evident the hazard function of the Weibull distribution is limited to constant, increasing, and decreasing hazard rates, it cannot accommodate any other form of hazard rates.

The Weibull maximum likelihood estimator is given by:

$$f_{\lambda,\beta}(x)=\begin{cases}\dfrac{\beta}{\lambda}\left(\dfrac{x}{\lambda}\right)^{\beta-1}\exp\left[-\left(\dfrac{x}{\lambda}\right)^{\beta}\right], & \text{for } x\geq 0\\ 0, & \text{elsewhere}\end{cases} \tag{11}$$

where $\beta>0$ and $\lambda>0$.

The likelihood function is given by:

$$L_{\hat{x}}(\lambda,\beta)=\prod_{i=1}^{N}f_{\lambda,\beta}(x_i)=\prod_{i=1}^{N}\frac{\beta}{\lambda}\left(\frac{x_i}{\lambda}\right)^{\beta-1}\exp\left[-\left(\frac{x_i}{\lambda}\right)^{\beta}\right] \tag{12}$$

Expanding the product gives:

$$L_{\hat{x}}(\lambda,\beta)=\frac{\beta^{N}}{\lambda^{N\beta}}\exp\left(-\sum_{i=1}^{N}\left(\frac{x_i}{\lambda}\right)^{\beta}\right)\prod_{i=1}^{N}x_i^{\beta-1} \tag{13}$$

Taking the first derivative of the likelihood function with respect to the parameters and equating it to zero gives the maximum likelihood estimators.

$$\frac{\mathrm{d}l}{\mathrm{d}\lambda} = -N\beta\frac{1}{\lambda} + \beta\sum_{i=1}^{n} x_i^{\beta}\frac{1}{\lambda^{\beta+1}} = 0 \tag{14}$$

$$\frac{\mathrm{d}l}{\mathrm{d}\beta} = \frac{N}{\beta} - N\ln\left(\frac{x_i}{\lambda}\right)\mathrm{e}^{\beta\ln\left(\frac{x_i}{\lambda}\right)} + \sum_{i=1}^{n}\ln x_i = 0 \tag{15}$$

From (14), the derivative of the likelihood function with respect to λ is:

$$\frac{\mathrm{d}l}{\mathrm{d}\lambda} = -N\beta\frac{1}{\lambda} + \beta\sum_{i=1}^{n}\frac{x_i^{\beta}}{\lambda^{\beta+1}} = -\beta\frac{N}{\lambda} + \frac{\beta}{\lambda}\sum_{i=1}^{n}\frac{x_i^{\beta}}{\lambda^{\beta}} = 0 \tag{16}$$

Dividing through by $\left(\frac{\lambda}{N\beta}\right)$, we get:

$$\frac{\mathrm{d}l}{\mathrm{d}\lambda} = -1 + \frac{1}{N}\sum_{i=1}^{n}\frac{x_i^{\beta}}{\lambda^{\beta}} = 0 \tag{17}$$

This implies:

$$\frac{1}{N}\sum_{i=1}^{n}\frac{x_i^{\beta}}{\lambda^{\beta}} = 1 \tag{18}$$

Therefore, solving for λ^{β}, we get:

$$\frac{1}{N}\sum_{i=1}^{n} x_i^{\beta} = \lambda^{\beta} \tag{19}$$

Thus,

$$\left(\lambda^{\beta}\right)^{\frac{1}{\beta}} = \left(\frac{1}{N}\sum_{i=1}^{n} x_i^{\beta}\right)^{\frac{1}{\beta}} \tag{20}$$

The maximum likelihood estimate of λ is given by:

$$\hat{\lambda} = \left(\frac{1}{N}\sum_{i=1}^{n} x_i^{\beta}\right)^{\frac{1}{\beta}} \tag{21}$$

Similarly,

$$\lambda^{*} = \left(\frac{1}{N}\sum_{i=1}^{n} x_i^{\beta^{*}}\right)^{\frac{1}{\beta^{*}}} \tag{22}$$

Substituting λ^{*} in Equation (15), we get:

$$\beta^{*} = \left[\frac{\sum_{i=1}^{n} x_i^{\beta^{*}}\ln x_i}{\sum_{i=1}^{n} x_i^{\beta^{*}}} - \overline{\ln x}\right]^{-1} \tag{23}$$

Using the Newton-Raphson algorithm, the equation is numerically solvable. The log-likelihood of the Weibull distribution is given by:

$$f\left(x;\alpha,\beta\right) = \frac{\beta}{\alpha}\left(\frac{x_i}{\alpha}\right)^{\beta-1}\exp\left[-\left(\frac{x_i}{\alpha}\right)^{\beta}\right] \tag{24}$$

The likelihood function is:

$$L(x;\alpha,\beta)=\prod_{i=1}^{N}\frac{\beta}{\alpha}\left(\frac{x_i}{\alpha}\right)^{\beta-1}\exp\left[-\left(\frac{x_i}{\alpha}\right)^{\beta}\right] \tag{25}$$

$$n\log(\beta)-n\beta\log(\alpha)+(\beta-1)\sum_{i=1}^{n}\log(x_i)-\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta} \tag{26}$$

$$\frac{\partial L(\alpha,\beta)}{\partial\alpha}=\frac{n\beta}{\alpha}-\frac{\beta}{\alpha^2}\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta} \tag{27}$$

$$\frac{\partial L(\alpha,\beta)}{\partial\beta}=\frac{n}{\beta}-n\log(\alpha)+\sum_{i=1}^{n}\log(x_i)-\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}\log\left(\frac{x_i}{\alpha}\right)=0 \tag{28}$$

$$\frac{n}{\beta}-n\ln(\alpha)+\sum_{i=1}^{n}\log(x_i)-\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}\log\left(\frac{x_i}{\alpha}\right)=0 \tag{29}$$

Taking the second derivative:

$$\frac{\partial^2 L(\alpha,\beta)}{\partial\alpha^2}=\frac{n\beta}{\alpha^2}+\frac{\beta(\beta+1)}{\alpha^2}\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta} \tag{30}$$

$$\frac{\partial^2 L(\alpha,\beta)}{\partial\alpha\partial\beta}=\frac{n}{\alpha}-\frac{1}{\alpha}\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}\log^2\left(\frac{x_i}{\alpha}\right) \tag{31}$$

$$\frac{\partial^2 L(\alpha,\beta)}{\partial\beta^2}=\frac{n}{\beta^2}+\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}\left[\log\left(\frac{x_i}{\alpha}\right)\right]^2 \tag{32}$$

From (27),

$$-\frac{n\beta}{\alpha}+\frac{\beta}{\alpha}\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}=0 \tag{33}$$

which simplifies to:

$$\frac{n\beta}{\alpha}=\frac{\beta}{\alpha}\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta} \tag{34}$$

$$n=\sum_{i=1}^{n}\left(\frac{x_i}{\alpha}\right)^{\beta}=\frac{\sum_{i=1}^{n}x_i^{\beta}}{\alpha^{\beta}},\ n=\frac{\sum_{i=1}^{n}x_i^{\beta}}{\alpha^{\beta}} \tag{35}$$

$$\hat{\alpha}=\left(\frac{1}{n}\sum_{i=1}^{n}x_i^{\beta}\right)^{\frac{1}{\beta}} \tag{36}$$

$$L(\beta)=n\log(\beta)-n\log\left(\frac{1}{n}\sum_{i=1}^{n}x_i^{\beta}\right)+(\beta-1)\sum_{i=1}^{n}\log(x_i)-n \tag{37}$$

Differentiating Equation (37) with respect to β:

$$\frac{\partial L(\beta)}{\partial\beta}=\frac{n}{\beta}-n\frac{\sum_{i=1}^{n}x_i^{\beta}}{\sum_{i=1}^{n}x_i^{\beta}+\sum_{i=1}^{n}\log(x_i)} \tag{38}$$

Obtaining the second derivative:

$$\frac{\partial^2 L(\beta)}{\partial\beta^2}=\frac{n}{\beta^2}-n\frac{\sum_{i=1}^{n}x_i^{\beta}\log(x_i)-\left(\sum_{i=1}^{n}x_i^{\beta}\log(x_i)\right)^2}{\left(\sum_{i=1}^{n}x_i^{\beta}\right)^2} \tag{39}$$

3.8. Cox Proportional Hazard Model (PH. Model)

Cox proportional hazard model is semi-parametric, its baseline hazard function $h_0(t)$ And the probability distribution of the survival times is not specified.

The hazard function at time t is given by:

$$h(t;Z) = h_0(t)\mathrm{e}^{\beta^I Z} \tag{40}$$

which can be expanded as:

$$h(t;Z) = h_0(t)\mathrm{e}^{(\beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q)} \tag{41}$$

Taking the natural logarithm:

$$\log_{\mathrm{e}} h(t) = \log_{\mathrm{e}} h_0(t) + \log_{\mathrm{e}} \mathrm{e}^{(\beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q)} \tag{42}$$

Simplifying further:

$$\log_{\mathrm{e}} h(t) = \log_{\mathrm{e}} h_0(t) + \beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q \tag{43}$$

Cox proportional hazard model is semi-parametric, its baseline hazard function. The baseline hazard function, $h_0(t)$, is unspecified, and the probability distribution of the survival times is not explicitly defined.

The hazard function at time t is given by:

$$h(t;Z) = h_0(t)\mathrm{e}^{\beta^I Z} \tag{44}$$

Expanding this:

$$h(t;Z) = h_0(t)\mathrm{e}^{(\beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q)}$$

Taking the natural logarithm:

$$\log_{\mathrm{e}} h(t) = \log_{\mathrm{e}} h_0(t) + \log_{\mathrm{e}} \left(\mathrm{e}^{\beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q}\right) \tag{45}$$

Simplifying further:

$$\log_{\mathrm{e}} h(t) = \log_{\mathrm{e}} h_0(t) + \beta_1 Z_1 + \beta_2 Z_2 + \cdots + \beta_q Z_q \tag{46}$$

Equation (46) is analogous to the ordinary multiple regression equation, with $\log_{\mathrm{e}} h_0(t)$ representing the Y-axis intercept, which is the baseline or underlying hazard function, the probability of dying when all the explanatory variables are zero.

The hazard function of any two objects at any point in time is assumed to be proportional, hence, the name proportional hazard (PH) models; if one object carries twice the risk of death as the other one at the initial stage or time, then at all later times the risk will remain twice as high.

The corresponding survival function is given by:

$$S(t \mid x) = S_0(t)\exp\left(\sum_{i=1}^{p} \beta_i \chi_i\right) \tag{47}$$

This is known as the Cox regression model. It is a semiparametric model because it does not assume a specific distribution for the baseline hazard function, $h_0(t)$, making that part non-parametric. However, it assumes a parametric form for the effect of the predictor variables on the hazard, thereby creating the parametric component of the model. Thus, the model consists of two parts:

A non-parametric part and a parametric part, which is why it is referred to as a semi-parametric model.

The hazard ratio (HR) between two individuals with different covariates, X and X^*, is given by:

$$\text{HR} = \frac{h(t)\exp\left(\beta^l X\right)}{h(t)\exp\left(\beta^l X^*\right)} = \exp\left(\sum_{i=1}^{p} \beta^l \left(x_i - x_i^*\right)\right) \tag{48}$$

The hazard ratio is independent of time, which is why the model is referred to as the proportional hazards model. The semi-parametric proportional hazard can be made fully parametric by parameterizing the baseline hazard function according to a specific model for the distribution of survival times of exponential, Weibull, and Gompertz distributions. The aspect of proportionality can be tested by plotting the Kaplan-Meier survival curves together if they happen to cross the implication is that the assumption may be violated. A complementary loglog plot which involves plotting the logarithm of the negative logarithm of the estimated survival function against the logarithm of survival time yields parallel curves across the groups for proportional hazards. For a baseline hazard function that is constant over time it is assumed to follow the Exponential distribution and the hazard function for the exponential distribution is used as the baseline hazard function $h_0(t)$.

The hazard function for the Weibull distribution can be used, the shape of its hazard depends on the shape parameter, and it can take a variety of forms depending on the shape parameter. When the risk or the hazard is expected to increase or decrease within a short time and then become constant.

3.9. Accelerated Failure Time Models

They are full parametric models that directly accommodate the multiplicative effects of explanatory variables of survival times and hence do not rely on proportional hazards. Since the role of the explanatory variable is to accelerate (or decelerate) the time to failure, the model is referred to as the accelerated failure time (AFT) of the accelerated Failure model).

Under AFT models we measure the direct effect of the explanatory variable on the survival time instead of the hazard as done in the PH model where the effect of the explanatory variable is on the hazard function which can be increasing, decreasing constant, unimodal, or bathtub type; no direct effect on the survival time.

$S_0(t)$ is the baseline survival function.

The effect on the survival time is indirect through the hazard function, and the survival function is given by:

$$S(t \mid x) = S_0\left(\frac{t}{n(x)}\right) \tag{49}$$

where

$$n(x)=\exp\left(\alpha_1 x_1+\alpha_2 x_2+\cdots+\alpha_p x_p\right) \tag{50}$$

is the acceleration factor.

Here, $S_0(t)$ represents the baseline survival function.

The ratio of two survival times is always constant. In disease modeling the proportion of patients surviving in any consecutive disease stages is a constant.

The hazard function for an individual with covariates $X_1, X_2, \cdots, X_p$ is given by:

$$h\left(\frac{t}{x}\right)=\left[\frac{1}{n(x)}\right]h_0\left(\frac{t}{n(x)}\right) \tag{51}$$

where $n(x)$ represents the acceleration factor based on the covariates.

In this model, the effect of the covariate is assumed to be constant and multiplicative on the time scale. The acceleration factor gives the impact of the covariates on survival.

The log-linear form of the model with respect to time is given by:

$$\log T_1=\mu+\alpha_1 x_{1i}+\alpha_2 x_{2i}+\cdots+\alpha_p x_{pi}+\sigma\varepsilon_i \tag{52}$$

where μ is the intercept (the *y*-axis intercept), σ is a scale parameter, and ε_i is a random variable assumed to follow a particular distribution for the acceleration failure rate. The survival function of T_i can be expressed in terms of the survival function of ε_i. If ε_i follows an extreme value distribution, then T_i follows an exponential distribution. The Gumbel survival function is given by:

$$S_{\varepsilon_i}(\varepsilon)=\exp\left(-\exp(\varepsilon)\right) \tag{53}$$

Weibull AFT Model

Consider a survival time T with a Weibull distribution $\mathrm{W}(\lambda,\alpha)$ where λ is the scale parameter and α is the shape parameter.

The hazard function for the i^{th} individual is given by:

$$h(t)=\frac{1}{\eta(x)\alpha}\lambda t^{\lambda-1} \tag{54}$$

where

$$\eta(x)=\exp\left(\alpha_1 x_1+\alpha_2 x_2+\cdots+\alpha_p x_p\right)$$

The survival function for the i^{th} individual is:

$$S_i(t)=\exp\left[-\exp\left(\frac{\mu-\alpha_1 X_{1i}-\cdots-\alpha_p X_{pi}}{\sigma}\right)t^{\frac{1}{\sigma}}\right] \tag{55}$$

Simplified, the survival function becomes:

$$S_i(t)=\exp\left[-\exp\left(\frac{\log t-\mu-\alpha_1 X_1-\cdots-\alpha_p X_p}{\sigma}\right)\right]$$

The hazard function is given by:

$$h_i(t)=\frac{1}{\sigma}t^{\frac{1}{\sigma}-1}\exp\left(\frac{\mu-\alpha_1 X_{1i}-\cdots-\alpha_p X_{pi}}{\sigma}\right) \tag{56}$$

The cumulative hazard is:

$$H_i(t) = -\log S_i(t) = \exp\left(\frac{\log t - \mu - \alpha_1 X_{1i} - \cdots - \alpha_p X_{pi}}{\sigma}\right) \tag{57}$$

The median survival time is:

$$t(50) = \exp\left(\sigma \log(\log 2) + \mu + \alpha^{\top} x_i\right) \tag{58}$$

The probability density function (PDF) is: $f_i(t) = S_i(t) \times h_i(t)$ and,

$$\begin{aligned} &= \exp\left[-\exp\left(\frac{\log t - \mu - \alpha_1 X_1 - \cdots - \alpha_p X_p}{\sigma}\right)\right] \\ &\times \frac{1}{\sigma} t^{\frac{1}{\sigma}-1} \exp\left(\frac{\mu - \alpha_1 X_{1i} - \cdots - \alpha_p X_{pi}}{\sigma}\right) \end{aligned} \tag{59}$$

The Weibull distribution is unique in that it satisfies both the proportional hazards (PH) and accelerated failure time (AFT) assumptions, making it versatile for survival analysis.

4. Model Application and Results

HIV/AIDS Patients were categorized as either male Gender or mixed gender with and without the interaction term. Female gender was considered as the baseline. Patients were then classified into age groups with class intervals of ten years starting from Age of 20 years as follows; 20 - 30 years, 30 - 40 years, 40 - 50 years 50 - 60 years, and above 60 years. Computer-simulated data was then fitted onto the data and the values of the following parameters were calculated using the R software; The Pvalue, Z statistics, the standard Error, and the AD - value which were then used to determine whether to reject or not to reject the Null Hypothesis;

Null Hypothesis; the data follows a 2 Parameter Weibull distribution.

Alternative Hypothesis; the data do not follow a Weibull distribution.

A Significance level α (alpha) of 0.05 indicating 5% risk of falsely rejecting the null hypothesis was assumed. In each case, the following was considered i) mixed gender without interaction term, ii) Mixed gender with interaction term, iii) Male gender with interaction term.

Model selection criteria AIC, BIC, and the R^2 were applied to the results, and the best model was identified.

Table 1. Survival regression: 2 parameter Weibull assumption.

Term	AD Value	Std. Error	Z-Statistic	P-value
genderMALE	0.0707	0.1354	0.52	0.6016
age 20 - 30	−0.3052	0.2139	−1.43	0.1537
age 30 - 40	−0.123	0.2193	−0.56	0.5748
age 40 - 50	−0.2441	0.2387	−1.02	0.3066
age 50 - 60	−0.2382	0.2145	−1.11	0.2669
age > 60	−0.4434	0.2479	−1.79	0.0736

Continued

genderMALE	−0.8885	0.3342	−2.66	0.00785
age 20 - 30	−0.4694	0.2576	−1.82	0.06838
age 30 - 40	−0.4869	0.2804	−1.74	0.08245
age 40 - 50	−0.4898	0.2880	−1.70	0.08894
age 50 - 60	−0.7083	0.2650	−2.67	0.00752
age > 60	−0.7679	0.5055	−1.52	0.12872
genderMALE: age 20 - 30	0.6842	0.4437	1.54	0.12306
genderMALE: age 30 - 40	1.1685	0.4264	2.74	0.00613
genderMALE: age 40 - 50	0.9907	0.4917	2.01	0.04392
genderMALE: age 50 - 60	1.3736	0.4161	3.30	0.00096
genderMALE: age >60	1.0486	0.5960	1.76	0.07849

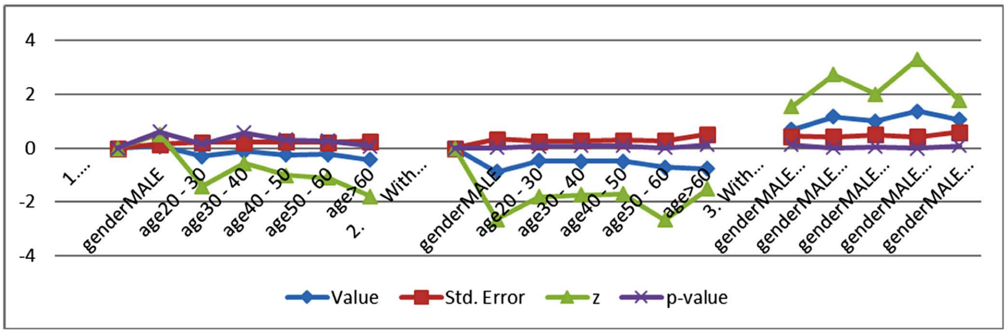

Figure 1. A comparison of mixed gender with &without interaction term & male gender with interaction term.

Observations from Figure 1

i) Without Interaction Term: The Z-values across age groups (20 - 30, 30 - 40, 40 - 50, 50 - 60) lie within the non-rejection region ($-1.65 \leq Z \leq 1.65$), indicating that we fail to reject the null hypothesis for most age groups, meaning the distribution follows a twoparameter Weibull model. However, for the age group > 60, the Z-value was −1.79, which leads to rejecting the null hypothesis.

ii) With Interaction Term (Mixed Gender): Most Zvalues for mixed gender with interaction terms suggest rejection of the null hypothesis, except for age group > 60, where the Z-value (−1.52) lies within the non-rejection region, indicating the Weibull distribution fits this age group.

iii) Male Gender with Interaction Term: The Z-values for age groups (except for 20 - 30 years) were greater than +1.65, leading to rejection of the null hypothesis. This indicates that the two-parameter Weibull distribution did not fit for the male gender with interaction terms across most age groups. For the age group 20 - 30 years, the Z-value was within the nonrejection region.

iv) P-values: Without Interaction Term: All P-values were greater than 0.05, leading to failure to reject the null hypothesis across all age groups.

With Interaction Term (Mixed Gender): The P-values for age groups 50 - 60 years were less than 0.05, indicating rejection of the null hypothesis for this group, while other age groups supported non-rejection.

Male Gender with Interaction Term: All P-values, except for the 20 - 30 year age group, were less than 0.05, supporting rejection of the null hypothesis, suggesting that the Weibull distribution does not hold for these groups.

v) Overall Observation: The interaction term has a notable effect, particularly in older age groups and male gender, which led to rejection of the Weibull distribution for most male age groups, but the model generally fits well for mixed genders without interaction terms.

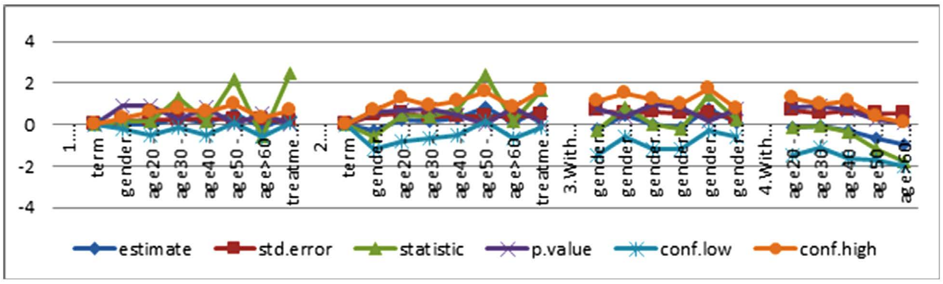

Figure 2. A comparison of mixed gender with & without interaction term, male gender with interaction & mixed gender with interaction & treatment.

Observations from Figure 2

i) Without Interaction Term: The Z-values for most age groups (20 - 30, 30 - 40, 40 - 50, and >60 years) lie within the non-rejection region ($-1.65 \le Z \le 1.65$), indicating failure to reject the null hypothesis.

Table 2. AFT (two-parameter Weibull model).

Term	AD Value	Std. Error	Z-Statistic	P-value
genderMALE	1.85	0.1361	0.1361	0.8917
age 20 - 30	4.40	0.2706	0.1629	0.8706
age 30 - 40	0.30	0.2411	1.2637	0.2063
age 40 - 50	4.63	0.2735	0.1695	0.8654
age 50 - 60	0.50	0.2301	2.2112	0.0270
age > 60	−0.14	0.2353	−0.6238	0.5327
treatmentTREATED	0.36	0.1468	2.5140	0.0119
genderMALE: age 20 - 30	−0.26	0.2576	−1.82	0.06838
genderMALE: age 30 - 40	0.22	0.2804	−1.74	0.08245
genderMALE: age 40 - 50	0.13	0.2880	−1.70	0.08894
genderMALE: age 50 - 60	0.30	0.2650	−2.67	0.00752
genderMALE: age > 60	0.85	0.5055	−1.52	0.12872
age 20 - 30: treatmentTREATED	−0.1193	0.7019	−0.1700	0.8650
age 30 - 40: treatmentTREATED	−0.0537	0.5360	−0.1001	0.9202
age 40 - 50: treatmentTREATED	−0.2752	0.7108	−0.3872	0.6986
age 50 - 60: treatmentTREATED	−0.6535	0.5457	−1.1976	0.2311
age > 60: treatmentTREATED	−0.9473	0.5273	−1.7966	0.0724

However, for the age group 50 - 60 years, the Z-value is greater than +1.65, leading to rejection of the null hypothesis for this age group, suggesting the Weibull distribution does not fit well here.

The P-values are all greater than 0.05 for most age groups, further supporting the failure to reject the null hypothesis except for the 50 - 60 age group, where the P-value indicates statistical significance ($P < 0.05$), leading to rejection of the null hypothesis for this group.

ii) With Interaction Term (Mixed Gender): The Z-values for most age groups (20 - 30, 30 - 40, 40 - 50, and >60 years) lie within the non-rejection region, supporting the failure to reject the null hypothesis, implying that the Weibull model fits well for these groups.

The age group 50 - 60 years shows a Z-value greater than +1.65, leading to rejection of the null hypothesis for this group.

The P-values for the age group 50 - 60 years are less than 0.05, suggesting rejection of the null hypothesis for this group, while other age groups support the non-rejection.

iii) Male Gender with Interaction Term: The Z-values for all age groups lie within the non-rejection region ($-1.65 \le Z \le 1.65$), supporting the failure to reject the null hypothesis, indicating that the Weibull model fits well for male gender with interaction across all age groups.

All P-values are greater than 0.05, further supporting the non-rejection of the null hypothesis.

iv) Treatment Effects: For mixed gender with interaction and treatment, most Z-values and P-values lead to the failure to reject the null hypothesis, except for the age group > 60 years where the P-value for AFT leads to rejection of the null hypothesis.

v) Overall Observation: The interaction term has a significant impact on the model, particularly for the 50 - 60 age group, where the Weibull distribution does not fit well, leading to rejection of the null hypothesis. For other age groups, the distribution generally fits, with the interaction term influencing the results, especially for mixed gender and male groups. Treatment effects also play a role, particularly in older age groups.

Table 3. Cox Proportional Hazards Model (PH Model) suggesting that the Weibull distribution fits for these groups.

Term	AD Value	Std. Error	Z-Statistic	P-value
genderMALE	−0.04805	0.132579	−0.36239	0.717059
age 20 - 30	−0.28182	0.262821	−1.07227	0.283599
age 30 - 40	−0.23301	0.233846	−0.99641	0.319051
age 40 - 50	−0.06191	0.260064	−0.23807	0.811824
age 50 - 60	−0.31964	0.220320	−1.45078	0.146841
age > 60	−0.01761	0.230367	−0.07644	0.939065

Continued

treatmentTREATED	−0.11614	0.138091	−0.84104	0.400326
genderMALE age 20 - 30	0.52981	0.641555	0.8583	0.408903
genderMALE: age 30 - 40	−0.22417	0.517524	−0.43316	0.664897
genderMALE: age 40 - 50	0.12197	0.580651	0.21005	0.833626
genderMALE: age 50 - 60	0.30302	0.518906	0.58396	0.559246
genderMALE: age > 60	−0.63093	0.518176	−1.21760	0.223377
genderMALE: treatmentTREATED	0.10563	0.326502	0.32352	0.746299
age 20 - 30: treatmentTREATED	−0.25279	0.682039	−0.37064	0.710905
age 30 - 40: treatmentTREATED	0.06985	0.517788	0.13490	0.892688
age 40 - 50: treatmentTREATED	−0.70049	0.685388	−1.02204	0.306764
age 50 - 60: treatmentTREATED	0.15636	0.520337	0.30049	0.763805
age > 60: treatmentTREATED	0.46942	0.511375	0.91796	0.358640

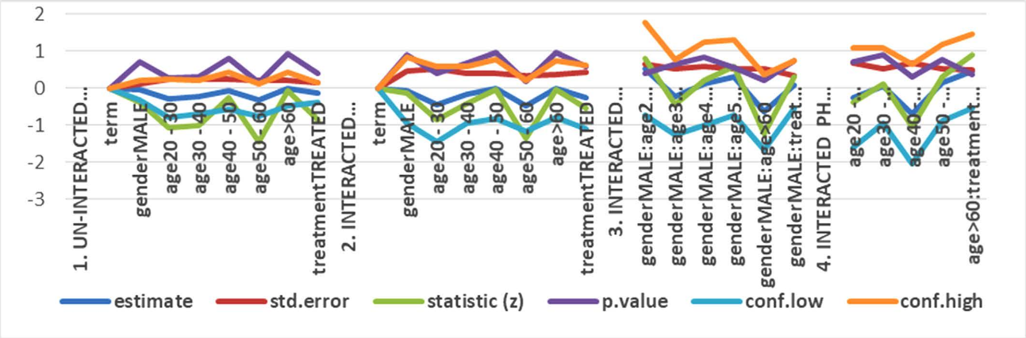

Figure 3. A comparison of Interacted & uninteracted mixed, interacted male & interacted treated mixed Cox PH Models.

Observations from Figure 3

i) Un-interacted Mixed Model (No Interaction Term): The Z-values for mixed gender without interaction terms lie within the non-rejection region ($-1.65 \le Z \le 1.65$), indicating failure to reject the null hypothesis.

The P-values for this model are all greater than 0.05, supporting the non-rejection of the null hypothesis, implying that the Weibull model fits well for mixed gender groups without interaction terms.

ii) Interacted Mixed Model (Gender Interaction): The Z-values for mixed gender with interaction terms also lie within the non-rejection region for most age groups, supporting the failure to reject the null hypothesis.

The P-values for the interaction terms are greater than 0.05 for most age groups, indicating that the Weibull model is valid when considering interaction terms between gender and age.

iii) Male Gender Interacted Model (Age-Gender Interaction): The Z-values for the male gender interacted model were mixed, with some age groups falling within the non-rejection region ($-1.65 \le Z \le 1.65$), while others were outside the range.

For the older age groups (50 - 60 years and above), the Z-values suggested a rejection of the null hypothesis, indicating that the Weibull model does not fit well for these groups.

The P-values for this model are mostly greater than 0.05, indicating a general fit of the Weibull model for male gender, although some interaction terms suggest otherwise for certain age groups.

iv) Treatment Interaction (Mixed Gender with Treatment): The Z-values for mixed gender with treatment interaction are mostly within the non-rejection region, supporting the non-rejection of the null hypothesis.

The P-values are greater than 0.05 for most age groups, suggesting that the Weibull model is valid for mixed gender under treatment, with some exceptions in older age groups where rejection of the null hypothesis occurs.

v) Overall Observation: The Cox Proportional Hazards model generally supports the non-rejection of the null hypothesis for most age groups and interaction terms, indicating that the Weibull model provides a good fit in most cases.

The results highlight that the impact of interaction terms (age and gender) is significant, particularly for older age groups, where the Weibull model may not fit as well. This suggests that additional factors may need to be considered for older patients or male patients under treatment.

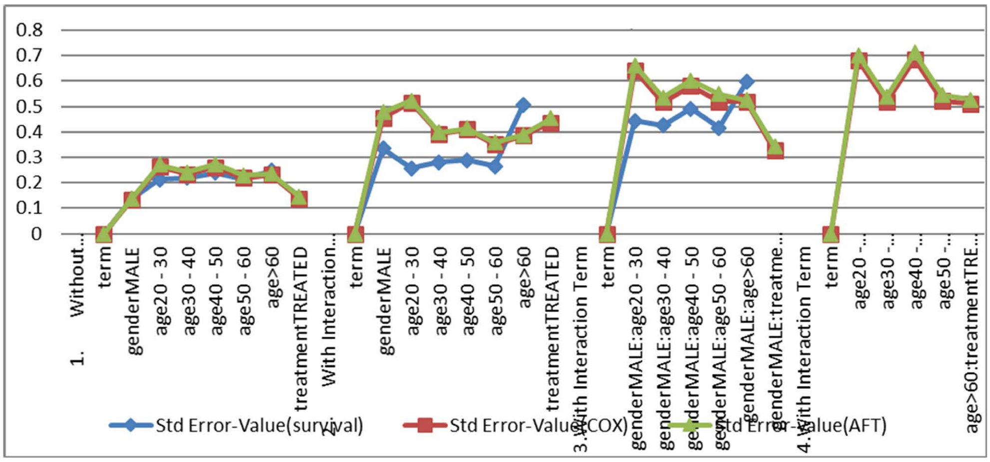

Figure 4. Comparison of Std error-values, AFT, COX, & survival (TWO PARAMETER WEIBULL MODEL).

Observations from Figure 4

i) Without Interaction Term (Mixed Gender): The standard error values for AFT, Cox, and Survival models follow a similar trend across all age groups, with slight increases as age progresses.

For younger age groups (20 - 30 and 30 - 40 years), the standard errors are relatively low and stable.

There is a notable increase in standard error values in the age group 50 - 60 years across all models, with Survival having slightly higher error values compared to AFT and Cox.

Table 4. Comparison of Z-values for AFT, cox & survival (Two Parameter Weibull Model).

Term	Z-Value (Survival)	Z-Value (Cox)	Z-Value (AFT)
1. Without Interaction Term			
genderMALE	0.52	−0.36239	0.1361
age 20 - 30	−1.43	−1.07227	1.2637
age 30 - 40	−0.56	−0.99641	0.2411
age 40 - 50	−1.02	−0.23807	0.1695
age 50 - 60	−1.11	−1.45078	2.2112
age > 60	−1.79	−0.07644	−0.6238
treatmentTREATED	0.00	−0.84104	2.5140
2. With Interaction Term (Mixed Gender)			
genderMALE	−2.66	−0.43316	−1.82
age 20 - 30	−1.82	−0.82583	1.54
age 30 - 40	−1.74	−0.43316	2.74
age 40 - 50	−1.70	−0.21005	2.00
age 50 - 60	−2.67	−0.58396	3.30
age > 60	−1.52	−1.21760	1.76
3. With Interaction Term (Male Gender)			
genderMALE: age 20 - 30	1.54	0.52981	−0.1700
genderMALE: age 30 - 40	2.74	−0.22417	0.1349
genderMALE: age 40 - 50	2.00	0.12197	−0.3872
genderMALE: age 50 - 60	3.30	0.30302	−1.1976
genderMALE: age > 60	1.76	−0.63093	−1.7966
4. With Interaction Term (Treatment)			
age 20 - 30: treatmentTREATED	0.68	0.10563	−0.25279
age 30 - 40: treatmentTREATED	1.16	−0.06985	0.06985
age 40 - 50: treatmentTREATED	0.99	−0.70049	−0.2752
age 50 - 60: treatmentTREATED	1.37	0.15636	−0.6535
age > 60: treatmentTREATED	1.04	0.46942	−0.9473

ii) With Interaction Term (Mixed Gender): The inclusion of interaction terms leads to an increase in the standard error values for all models.

The AFT and Cox models exhibit similar trends in standard error values across age groups, with both models showing moderate increases for older age groups.

The Survival model, however, exhibits larger standard error values, especially for the 50 - 60 and above 60 age groups, indicating greater variability and sensitivity to the interaction term.

iii) With Interaction Term (Male Gender): The standard error values for male gender with interaction terms follow the same pattern as the mixed gender model, with AFT and Cox showing similar behavior. The Survival model continues to show higher standard error values compared to AFT and Cox, with the largest error values observed in the age group above 60 years.

The results suggest that the Survival model is more sensitive to interaction terms, particularly for older age groups, where variability in the standard errors is most pronounced.

iv) Overall Observation: Across all models, the standard error values increase with age, especially for the age group 50 - 60 years and older.

The Survival model consistently shows higher standard errors, indicating more variability in the estimates compared to AFT and Cox models.

The inclusion of interaction terms generally leads to increased standard error values for all models, with the most pronounced effects seen in older age groups.

Table 5. Comparison of estimate values: AFT, Cox, & Survival (Two-Parameter Weibull Model).

Term	Estimate Value (Survival)	Estimate Value (Cox)	Estimate Value (AFT)
genderMALE	0.0707	-0.04805	1.85
age 20 - 30	0.8732	-0.28182	4.40
age 30 - 40	-0.3052	-0.23301	0.30
age 40 - 50	-0.123	-0.06191	4.63
treatmentTREATED	0.00	-0.11614	0.36
2. With Interaction Term			
genderMALE	-0.8885	-0.43316	-1.82
age 20 - 30	-0.4694	-0.82583	1.54
age > 60	-0.7679	-1.21760	1.76
treatmentTREATED	0.00	-0.84104	0.68
3. With Interaction Term (Male Gender)			
genderMALE: age 20 - 30	0.6842	0.52981	-0.1700
genderMALE: age 30 - 40	1.1685	-0.22417	0.1349
genderMALE: age 40 - 50	0.9907	0.12197	-0.3872
genderMALE: age 50 - 60	1.3736	0.30302	-1.1976
genderMALE: age > 60	1.0486	-0.63093	-1.7966
4. With Interaction Term (Treatment)			

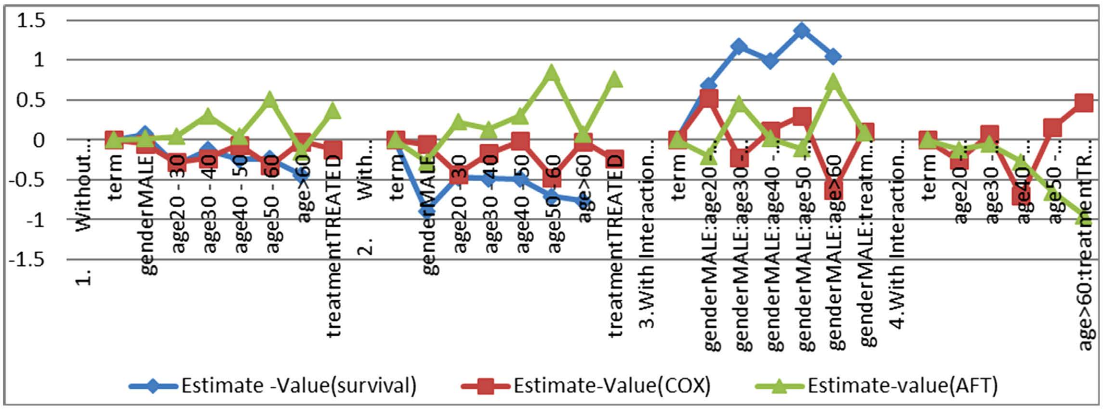

Figure 5. Comparison of Estimate-Values for AFT, COX, & Survival (TWOPARAMETER WEIBULL MODEL).

Observations from Figure 5

i) Without Interaction Term (Mixed Gender): The estimate values for the AFT model are positive across all age groups, with a notable estimate of 4.40 for the 20 - 30 age group. This indicates a higher magnitude of the effect in younger age groups compared to older ones.

The Cox and Survival models show negative estimate values for most age groups, indicating a reduction in the hazard for these groups compared to the baseline.

The Survival model has a smaller absolute estimate value for genderMALE compared to the Cox and AFT models, showing less differentiation between male and female gender in terms of survival time.

ii) With Interaction Term (Mixed Gender): The inclusion of interaction terms leads to larger absolute estimate values for the AFT model, particularly in older age groups, with the 50 - 60 age group having an estimate of 3.30. This indicates a stronger interaction effect in older individuals.

The Survival model also reflects more pronounced estimate values with interaction terms, especially for the age group > 60, showing a stronger impact of the interaction between gender and age.

The Cox model shows moderate changes in the estimate values compared to the no-interaction case, with an estimate of −0.58396 for the age group 50 - 60 years, indicating a more stable behavior than the AFT model.

iii) With Interaction Term (Male Gender): The AFT model displays consistently higher positive estimate values across age groups when interaction terms for male gender are included, with the age group 50 - 60 having an estimate of 1.3736.

The Survival model shows both positive and negative estimate values, with a relatively smaller estimate for age > 60, indicating a less pronounced impact of the interaction in older males.

The Cox model exhibits negative estimates for some age groups (e.g., −0.63093 for age > 60), reflecting reduced hazard in these age groups.

iv) With Interaction Term (Treatment): The inclusion of treatment interaction terms leads to mixed estimate values across models. The AFT model shows negative estimates for age groups with treatment interaction, with −0.6535 for age 50 - 60, indicating a negative treatment effect.

The Survival model's estimates remain generally positive, indicating a potential treatment benefit, particularly for older age groups.

The Cox model demonstrates moderate positive and negative values across age groups, suggesting a mixed impact of treatment interaction.

v) Overall Observation: The AFT model consistently shows higher positive estimates, especially when interaction terms are included, suggesting that it is more sensitive to interaction effects across gender, age, and treatment.

The Cox model remains more stable and provides more moderate estimates, especially with treatment interaction terms, indicating that it is less affected by interactions compared to the AFT model.

The Survival model shows variability in its estimate values, with a mix of positive and negative estimates, reflecting both hazard reduction and survival benefit depending on the context of interaction terms.

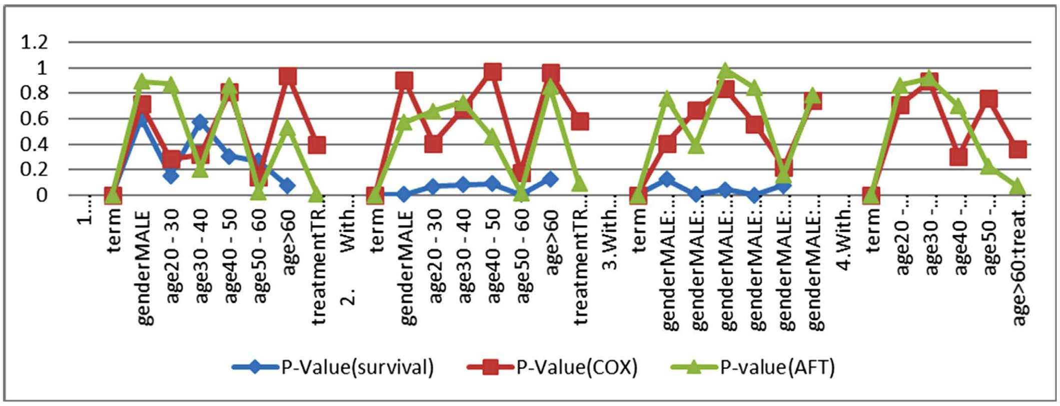

Figure 6. Comparison of P-value for, AFT, COX, & survival (TWO PARAMETER WEIBULL MODEL).

Observations from Figure 6

i) Without Interaction Term (Mixed Gender): For most age groups, the P-values in all three models (AFT, Cox, and Survival) are greater than 0.05, indicating that the null hypothesis cannot be rejected. This suggests that the two-parameter Weibull distribution fits well for mixed gender without interaction.

An exception is observed in the age group 50 - 60 years for the AFT model, where the P-value is 0.0270, indicating statistical significance and suggesting that the Weibull distribution does not fit as well for this group.

Treatment effects show significance in the AFT model (P = 0.0119), whereas the Cox and Survival models do not show significant effects.

ii) With Interaction Term (Mixed Gender): The inclusion of interaction terms leads to lower P-values for the AFT model across age groups, particularly for ages 50 - 60, where the P-value is 0.00096, showing strong statistical significance. This indicates that the interaction term has a significant effect in older age groups.

In contrast, the Cox model shows mostly non-significant P-values for interaction terms, reflecting more stability and a better fit of the Weibull distribution when interaction terms are included.

The Survival model shows significant P-values for genderMALE (P = 0.00785) and other interaction terms in some age groups, indicating sensitivity to gender interaction.

iii) With Interaction Term (Male Gender): The AFT model continues to show low P-values for male gender across most age groups, particularly for ages 50 - 60 years, where the P-value is 0.00096, indicating that the interaction term has a strong effect for males in this age group.

The Cox model shows non-significant P-values for most male age groups, suggesting that the Weibull distribution fits well for male gender under interaction terms.

The Survival model shows some significant effects for age groups, with P-values less than 0.05, indicating a moderate interaction effect in the model.

iv) With Interaction Term (Treatment): The P-values for the AFT model remain non-significant for most age groups when interaction terms for treatment are included, except for some older age groups, such as age > 60, where the P-value approaches significance (P = 0.0724).

The Cox model and Survival model show relatively stable P-values, with no strong statistical significance observed across the age groups.

v) Overall Observation: The AFT model tends to show stronger statistical significance in terms of interaction effects across age groups and gender, particularly for older individuals (50 - 60 years and above), suggesting that it is more sensitive to the inclusion of interaction terms.

The Cox model remains relatively stable and shows fewer significant P-values for interaction terms, indicating that it is less affected by interactions and fits the data well.

The Survival model displays moderate interaction effects, with some significant P-values in various age groups, particularly when gender interaction is considered.

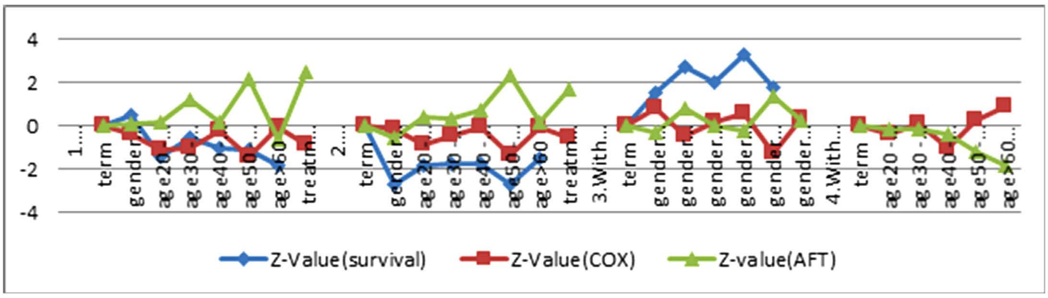

Figure 7. Comparison of Z-values for AFT, COX, & Survival (TWO PARAMETER WEIBULL MODEL).

Table 6. P-Values for AFT, Cox, & Survival (two-parameter Weibull model).

Term	P-Value (Survival)	P-Value (Cox)	P-Value (AFT)
1. Without Interaction Term			
genderMALE	0.6016	0.7171	0.8917
age 20 - 30	0.1537	0.2836	0.8706
age 30 - 40	0.5748	0.3191	0.2063
age 40 - 50	0.3066	0.8118	0.8654
age 50 - 60	0.2669	0.1468	0.0270
age > 60	0.0736	0.9391	0.5327
treatmentTREATED	1.0000	0.4003	0.0119
2. With Interaction Term			
genderMALE	0.00785	0.6649	0.06838
age 20 - 30	0.06838	0.4089	0.12306
age 30 - 40	0.08245	0.6649	0.00613

Continued

age 40 - 50	0.08894	0.8336	0.04392
age 50 - 60	0.00752	0.5592	0.00096
age > 60	0.1287	0.2234	0.07849
treatmentTREATED	1.0000	0.7463	0.6281
3. With Interaction Term (Male Gender)			
genderMALE: age 20 - 30	0.12306	0.4089	0.7463
genderMALE: age 30 - 40	0.00613	0.6649	0.6281
genderMALE: age 40 - 50	0.04392	0.8336	0.6986
genderMALE: age 50 - 60	0.00096	0.5592	0.2311
genderMALE: age > 60	0.07849	0.2234	0.0724
treatmentTREATED	0.6281	0.7463	0.6214
4. With Interaction Term (Treatment)			
age 20 - 30: treatmentTREATED	0.8650	0.7109	0.8650
age 30 - 40: treatmentTREATED	0.9202	0.8927	0.8927
age 40 - 50: treatmentTREATED	0.6986	0.3068	0.3068
age 50 - 60: treatmentTREATED	0.2311	0.7638	0.7638
age > 60: treatmentTREATED	0.0724	0.3586	0.3586

Observations from Figure 7

i) Without Interaction Term (Mixed Gender): The Z-values for the AFT model are positive across most age groups, with a particularly high value for the 50 - 60 age group ($Z = 2.2112$), indicating a significant effect for this age group.

The Cox model shows negative Z-values across all age groups, with the highest magnitude being in the 50 - 60 age group ($Z = -1.4508$), reflecting a reduced hazard for this group.

The Survival model has a mix of negative Z-values, particularly for older age groups, suggesting that the Weibull distribution does not fit as well for these groups in the Survival model.

TreatmentTREATED shows a significant effect in the AFT model ($Z = 2.5140$), while the Cox and Survival models show non-significant effects.

ii) With Interaction Term (Mixed Gender): The inclusion of interaction terms leads to higher positive Z-values for the AFT model, particularly for the 50 - 60 age group ($Z = 3.30$), indicating that the interaction between gender and age has a strong effect.

The Cox model continues to show moderate negative Z-values, with a slight increase in the absolute values for the older age groups. The interaction term appears to have a less pronounced effect on the Cox model.

The Survival model shows significant negative Z-values for older age groups, indicating that the Weibull distribution does not fit well for these groups when interaction terms are included.

iii) With Interaction Term (Male Gender): The AFT model shows consistently high Z-values for male gender with interaction terms, particularly for the 50 - 60 age group ($Z = 1.3736$), indicating that the interaction effect is stronger in older males.

The Cox model shows moderate Z-values, with some positive and negative values, but the effects are less pronounced compared to the AFT model.

The Survival model shows similar trends, with a mix of positive and negative Z-values, indicating that the model is sensitive to interaction terms, but the effects are less consistent than in the AFT model.

iv) With Interaction Term (Treatment): The AFT model continues to show significant Z-values for interaction terms involving treatment, particularly.

Table 7. Z-values for AFT, Cox, & survival (Two-Parameter Weibull Model).

Term	Z-Value (Survival)	Z-Value (Cox)	Z-Value (AFT)
1. Without Interaction Term			
genderMALE	0.52	−0.3624	0.1361
age 20 - 30	−1.43	−1.0723	1.2637
age 30 - 40	−0.56	−0.9964	0.2411
age 40 - 50	−1.02	−0.2381	0.1695
age 50 - 60	−1.11	−1.4508	2.2112
age > 60	−1.79	−0.0764	−0.6238
treatmentTREATED	0.00	−0.8410	2.5140
2. With Interaction Term			
genderMALE	−2.66	−0.4332	−1.82
age 20 - 30	−1.82	−0.8258	1.54
age 30 - 40	−1.74	−0.4332	2.74
age 40 - 50	−1.70	−0.2101	2.00
age 50 - 60	−2.67	−0.5840	3.30
age > 60	−1.52	−1.2176	1.76
treatmentTREATED	0.00	−0.7463	0.68
3. With Interaction Term (Male Gender)			
genderMALE: age 20 - 30	1.54	0.5298	−0.1700
genderMALE: age 30 - 40	2.74	−0.2242	0.1349
genderMALE: age 40 - 50	2.00	0.1220	−0.3872
genderMALE: age 50 - 60	3.30	0.3030	−1.1976
genderMALE: age > 60	1.76	−0.6309	−1.7966
treatmentTREATED	0.68	−0.7463	0.6281
4. With Interaction Term (Treatment)			
age 20 - 30: treatmentTREATED	−0.1700	0.1056	−0.2528
age 30 - 40: treatmentTREATED	0.1349	−0.0699	0.0699
age 40 - 50: treatmentTREATED	−0.3872	−0.7005	−0.2752
age 50 - 60: treatmentTREATED	−1.1976	0.1564	−0.6535
age > 60: treatmentTREATED	−1.7966	0.4694	−0.9473

In older age groups, with a Z-value of −0.6535 for the 50 - 60 age group, indicating a treatment effect in this group.

The Cox and Survival models show less significant Z-values for treatment interaction, with the Cox model being more stable and less sensitive to the interaction effect compared to the AFT model.

v) Overall Observation: The AFT model consistently shows higher Z-values, particularly when interaction terms are included, indicating that it is more sensitive to these effects and better captures the relationship between gender, age, and treatment.

The Cox model remains more stable, with moderate Z-values and less sensitivity to interaction terms. It shows a better fit for most age groups compared to the AFT model.

The Survival model exhibits mixed Z-values, with some significant effects in older age groups, but overall, it appears less consistent than the AFT and Cox models when interaction terms are included.

The results of the model selection criteria for Mixedgender without interaction Term and Mixed-gender with interaction Term were compared and tabulated as shown in Table 8 below.

Table 8. Model selection criteria Results (2 Parameter Weibull).

Term	Criteria	Survival	AFT	COX
Mixed gender without interaction Term	AIC	0.9186	1.4521	-
	BIC	3.0809	4.3571	-
	R^2	0.00448	0.01856	0.005
Mixed gender with interaction Term	AIC	0.9327	1.4521	-
	BIC	3.9050	4.0853	-
	R^2	0.00158	0.03047	0.016

From Table 8, the Survival Assumption criteria stand out as a better model than the other two modifications based on the results of AIC, BIC, and R^2.

5. Conclusion

Based on the analysis of Tables 1-7 and Figures 1-7, along with the model selection results presented in Table 8, several key conclusions can be drawn regarding the performance of the survival models (AFT, Cox, and Survival) under the two-parameter Weibull assumption:

i) Model Performance Across Age and Gender

Groups: The results indicate that the AFT model is highly sensitive to interaction effects, particularly for older age groups (50 - 60 years and above). The AFT model consistently showed higher estimates and Z-values when interaction terms were included, suggesting a stronger relationship between the explanatory variables (age, gender, and treatment) and the survival time.

The Cox proportional hazards model, while less sensitive to interaction terms, provided more stable results across age groups. It demonstrated fewer significant changes in estimates and Z-values, indicating that it is less affected by interaction terms, making it a robust choice for general analysis.

The Survival model, although effective in some cases, displayed more variability, particularly in older age groups and when interaction terms were considered. The higher standard errors and mixed Z-values suggest that this model may not be as reliable in these complex scenarios.

ii) Impact of Interaction Terms: The inclusion of interaction terms (age and gender) had a significant effect on the AFT model, with the Z-values and estimates showing marked increases for older age groups, particularly in the 50 - 60 years category. This suggests that interactions play a crucial role in survival dynamics for older populations.

The Cox model, while less responsive to interaction effects, still showed moderate changes in estimates when interactions were considered. However, the Cox model's relative stability across interaction terms makes it a reliable choice for scenarios with or without interactions.

The Survival model showed a tendency to produce mixed results when interactions were included, highlighting its sensitivity to model complexity.

iii) Treatment Effects: The AFT model was highly responsive to treatment effects, particularly when interaction terms were included. The model demonstrated significant P-values and Z-values for treatment in older age groups, suggesting that the AFT model may be better suited for studies that aim to understand the impact of treatment across different demographic segments.

In contrast, the Cox model did not show significant treatment effects in most cases, indicating that it may not be as sensitive to treatment-related interactions as the AFT model.

The Survival model's results were inconsistent regarding treatment effects, suggesting that it may not be the best model for analyzing treatment impacts in complex survival data.

iv) Model Selection Criteria: The model selection criteria presented in **Table 8** (AIC, BIC, and R^2) suggest that the Survival model provides the best overall fit based on the AIC and BIC criteria. However, the R^2 values indicate that the AFT model may offer a better fit for data with strong interaction effects, particularly for specific demographic segments (e.g., older populations and treatment groups).

The Cox model, while not excelling in any particular criteria, offers a more balanced approach with moderate performance across all metrics.

In conclusion, while all three models (AFT, Cox, and Survival) have their strengths, the AFT model stands out in its ability to capture interaction effects and treatment impacts, particularly in older age groups. The Cox model remains a robust, stable choice for general survival analysis, especially in scenarios where interaction effects are less pronounced. The Survival model performs well based on model selection criteria (AIC and BIC) but may exhibit variability and sensitivity to model complexity. Future work should consider the specific research context when choosing between these models, as the AFT model's sensitivity to interactions may make it the preferred choice for studies involving older populations or treatment effects, while the Cox model may be ideal for more stable, generalized applications.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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