ACCELERATED FAILURE TIME MODELING FOR PROGNOSTIC FACTORS IN MALE DIABETES PATIENTS: A COMPARATIVE ANALYSIS OF SURVIVAL MODELS

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Abstract

Accelerated Failure Time Models (AFTMs) are utilized to examine survival patterns, particularly in the context of diseases such as diabetes, where traditional models like Cox proportional hazards may not apply. In this study, we apply AFTMs to identify significant prognostic factors affecting survival in male diabetic patients, using parametric distributions such as Exponential, Weibull, Log-normal, and Log-logistic. The primary objective of this study is to gain deeper insights into how key covariates influence survival times and enhance risk stratification, ultimately leading to better treatment outcomes. We evaluated the fit of several AFTMs by comparing Log-Likelihood, Akaike Information Criterion (AIC), and Bayesian Information Criterion (BIC) values. Among the models tested, the Weibull AFTM emerged as the best fit, demonstrating superior Log-Likelihood and lower AIC and BIC values compared to other distributions. The study identified several significant predictors of survival in male diabetic patients, including age, family history of diabetes, duration of diabetes, early use of insulin (within one year of diagnosis), retinopathy, use of diuretics, proteinuria, hypertension, and fasting plasma glucose levels. All of these covariates were found to significantly influence survival outcomes ($P < 0.05$), with older age and longer diabetes duration correlating with poorer survival rates. These findings underscore the importance of using AFTMs to model survival patterns in diabetic patients and the potential for targeted interventions based on identified risk factors. While the small sample size limits the generalizability of the results, this study provides valuable insights into the survival characteristics of male diabetic patients and highlights the need for further research with larger datasets. Future studies should consider a wider range of covariates and explore the application of AFTMs in broader diabetic populations to refine survival prediction models and optimize patient care. Additionally, integrating machine learning techniques with AFTMs could enhance predictive accuracy and provide a more comprehensive understanding of survival trends in diabetic patients.

Keywords: Accelerated Failure Time Model, Survival Analysis, Diabetes Mellitus, Weibull Distribution, Exponential Distribution, Prognostic Factors, Survival Prediction, Parametric Models.

I. Introduction

The Accelerated Failure Time (AFT) regression model has gained increasing attention as an alternative to the Cox proportional hazards model, particularly when the assumption of proportional hazards is violated [1]. While the Cox model is widely used in survival analysis, it assumes that the hazard ratio between different covariate levels remains constant over time. However, in many real-world scenarios, this assumption may not hold, especially when dealing with diseases that exhibit time-varying effects. In such cases, the AFT model provides a more flexible framework by modeling the survival time directly and assessing how covariates accelerate or decelerate the life course of an individual or disease process. Unlike the Cox model, which focuses on hazard ratios, the AFT model provides a direct interpretation of how covariates affect survival time by accelerating or decelerating the life course of a disease. This approach is beneficial for understanding survival patterns and identifying key risk factors in various contexts, including studies involving male diabetes patients.

Several parametric distributions are commonly used within the AFT framework, with each offering specific advantages depending on the nature of the data [2]. The Exponential distribution, often considered a simple and straightforward choice, assumes a constant hazard rate and is typically used when there is little evidence of varying hazard rates over time. However, for more complex survival patterns, the Weibull distribution is often preferred as it accommodates both increasing and decreasing hazard rates, making it more flexible in capturing various survival dynamics [3]. The Log-normal and Log-logistic distributions, on the other hand, are more suited for situations where the survival times follow a skewed distribution or when the effects of covariates are expected to vary in a non-linear fashion. The Exponential and Weibull distributions share the dual property of being able to model both proportional hazards and accelerated failure times. This makes them particularly useful when the data exhibit characteristics of both models, allowing for a more comprehensive understanding of survival processes. On the other hand, the Log-normal and Log-logistic distributions are exclusively aligned with the AFT approach, providing a more direct interpretation of how covariates influence survival times without the assumption of proportional hazards.

Diabetes is a leading chronic disease in men, increasing morbidity and mortality worldwide [4]. Key risk factors include age, obesity, hypertension, dyslipidemia, smoking, inactivity, and poor glycemic control. Identifying prognostic indicators is crucial for risk stratification, early intervention, and optimized treatment, ultimately improving long-term health outcomes. Srividhya et al. in 2019 [5] compared different parametric modeling approaches for time-to-event data among cancer patients, contributing to more informed decision-making in clinical practice and developing targeted interventions to improve patient outcomes. Several researchers have employed the Accelerated Failure Time Model (AFTM) in survival analysis studies of diabetic patients. For instance, Tachkov et al. (2020) [6] conducted a retrospective observational study comparing life expectancy and survival rates between diabetic and non-diabetic populations in Bulgaria. Their findings revealed that individuals with diabetes had a higher relative risk of death compared to non-diabetic individuals. Additionally, Sharma et al. (2020) [7] explored cognitive impairments in type 2 diabetes, identifying poor lifestyle choices, advanced age, hyperglycemia, hypercholesterolemia, and inflammation as significant risk factors contributing to cognitive and memory impairments in diabetic patients. These studies underscore the utility of AFTMs in identifying critical risk factors and understanding survival patterns among diabetic patients. Juhan et al. (2016) [8] conducted a comparative analysis of the Cox model, Stratified Weibull model, and Weibull AFTM to examine the effects of various covariates.

In this study, we aim to analyze data on a specific subset of male diabetes patients, focusing on various characteristics, including clinical, pathological, survival, and prognostic

factors. Despite extensive research on diabetes [9, 10, 11], studies identifying the key predictors of overall survival in men with diabetes remain limited. Therefore, the objective of this paper is to determine the significant prognostic factors influencing overall survival in male diabetes patients using parametric AFT models.

II. Accelerated Failure Time Model

For a study involving n male diabetic patients, let T_i represent the survival time (in months) of the i^{th} patient as a non-negative random variable influenced by various covariates $x = (x_1, x_2, \ldots, x_p)$. The Accelerated Failure Time Model (AFTM) describes the logarithm of survival time T_i as:

$$\log(T_i) = \mu + \beta_1 x_1 + \cdots + \beta_p x_p + \sigma\varepsilon_i = \mu + \beta_r x + \sigma\varepsilon_i$$

Here, $\log(T_i)$ denotes the log-transformed survival time, μ is the intercept, $\beta_r = (\beta_1, \beta_2, \ldots, \beta_p)$ represents the vector of regression coefficients, σ is a scale parameter, and ε_i is a residual term. The residual term ε_i is assumed to follow specific distributions, such as the Extreme Value distribution (with σ=1 or a constant σ=c), Normal distribution, or Logistic distribution. These choices for ε_i correspond to Exponential, Weibull, Log-normal, and Log-logistic AFT models for the survival time T_i.

In modeling survival time T using ε, the survival function $S(t;x)$, hazard function $h(t;x)$, and cumulative hazard function $H(t;x)$ for a general AFTM can be expressed in terms of the baseline model and the random component ε. For patients with survival time T, the survival function is defined as:

$$S(t) = P(T \geq t) = P(logT \geq logt) = P\{\exp(\mu + \beta_r x + \sigma\varepsilon) \geq t\} = P\{\exp(\mu + \sigma\varepsilon) \geq t/\exp(\beta_r x)\}$$

If no covariates are present in the model (i.e., x=0), the survival function simplifies to:

$$S_0(t) = P\{\exp(\mu + \sigma\varepsilon) \geq t\}$$

For patients in a AFTM with covariates, the survival function becomes,

$$S(t;x) = S_0\{t/\exp(\beta_r x)\}$$

From the relationship between the hazard function and the cumulative hazard function, the hazard function can be expressed as:

$$h(t;x) = \exp(-\beta_r x)\, h_0\{t/\exp(\beta_r x)\}$$

Here, $S_0(.)$ and $h_0(.)$ denote the baseline survival and hazard functions, respectively, and $\exp(\beta_r x)$ represents the acceleration factor. The density function of a general AFTM in terms of ε is given by:

$$f(t,x) = \frac{1}{\sigma t} f_\varepsilon\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$

The survival function for patients with survival time T is defined as:

$$S(t;x) = P(\mu + \beta_r x + \sigma\varepsilon \geq log\ t) = P\left(\varepsilon \geq \left(\frac{logt - \mu - \beta_r x}{\sigma}\right)\right)$$

In terms of ε, the survival function for a general AFTM becomes:

$$S(t;x) = S_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$

Similarly, the hazard function in terms of ε for a general AFTM is expressed as:

$$h(t,x) = \frac{1}{\sigma t} h_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$

Here, $S_{\varepsilon}(\cdot)$ and $h_{\varepsilon}(\cdot)$ represent the survival and hazard functions associated with the distribution of ε, respectively.

I. Exponential AFTM

When ε follows an extreme value or double exponential distribution with $\sigma = 1$, the density function and survival function of ε are given by:

$$f_{\varepsilon}(\varepsilon) = exp\{\varepsilon - \exp(\varepsilon)\}$$
$$S_{\varepsilon}(\varepsilon) = exp\{-\exp(\varepsilon)\};\ -\infty < \infty$$

Under this assumption, the time variable T follows an Exponential AFTM, with the density function expressed as:

$$f(t;x) = exp\{-\mu + \beta_r x\} exp\{-exp[-(\mu + \beta_r x)]t\}; t > 0$$

The survival function for the exponential AFTM is:

$$S(t;x) = exp\{-exp[-(\mu + \beta_r x)]t\}$$

The hazard function for the Exponential AFTM is:

$$h(t;x) = exp\{-\mu + \beta_r x\}$$

II. Weibull AFTM

When the random component ε follows an extreme value distribution with a scale parameter $\sigma = c$ (a constant), the survival time T follows a Weibull distribution. The corresponding density function is given as:

$$f(t) = \frac{1}{\sigma} exp\left\{-\frac{\mu + \beta_r x}{\sigma}\right\} t^{\frac{1}{\sigma}-1} \times exp\left\{-exp\left(-\frac{\mu + \beta_r x}{\sigma}\right) t^{\frac{1}{\sigma}}\right\}, t > 0$$

The survival function for the Weibull AFTM is expressed as:

$$S(t;x) = S_{\boldsymbol{\varepsilon}}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right) = exp\left\{-exp\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)\right\}$$

The hazard function is derived as:

$$h(t;x) = \frac{1}{\sigma t} h_{\boldsymbol{\varepsilon}}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right) = \frac{1}{\sigma t} exp\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$

III. Log-Logistic AFTM

When ε follows a logistic distribution, the density and survival functions are defined as:

$$f_{\varepsilon}(\varepsilon) = \frac{\exp(\varepsilon)}{[1 + \exp(\varepsilon)]^2}$$
$$S_{\varepsilon}(\varepsilon) = \frac{1}{1 + \exp(\varepsilon)}, -\infty < \varepsilon < \infty$$

Under these conditions, the survival tike T follows a Log-logistic AFTM. Its density function can be written as:

$$f(t;x) = \frac{\exp(\theta) k t^{k-1}}{[1 + \exp(\theta) t^k]^2}, t > 0$$

The survival function for the log-logistic AFTM becomes:

$$S(t;x) = S_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$
$$= \left[1 + exp\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)\right]^{-1}$$
$$= \left[1 + t^{\frac{1}{\sigma}} exp\left(\frac{-\mu - \beta_r x}{\sigma}\right)^{-1}\right]$$
$$= [1 + t^k exp\{\theta - k(\beta_r x)\}]^{-1}$$

where $\theta = -\frac{\mu}{\sigma}$ and $k = \frac{1}{\sigma}$ are the parameters of the model. The hazard function for the Log-logistic AFTM is then given as:

$$h(t;x) = \frac{1}{\sigma t} h_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right) = \frac{1}{\sigma t}\left[1 + exp\left(-\frac{logt - \mu - \beta_r x}{\sigma}\right)\right]^{-1}$$

IV. Log-normal AFTM

If ε follows a standard normal distribution, the density function and survival function for ε are:

$$f_{\varepsilon}(\varepsilon) = \frac{1}{\sqrt{2\pi}} exp\left(-\frac{\varepsilon^2}{2}\right)$$
$$S_{\varepsilon}(\varepsilon) = 1 - \Phi(\varepsilon), -\infty < \varepsilon < \infty$$

where $\Phi(\cdot)$ is the standard normal cumulative distribution function. Under these assumptions, the survival time T follows a Log-normal AFTM, with its density function expressed as:

$$f(t;x) = \frac{exp\left\{-\left(\frac{(logt - \mu - \beta_r x)^2}{2\sigma^2}\right)\right\}}{\sigma t\sqrt{2\pi}}$$

The survival function for log-normal AFTM becomes:

$$S(t;x) = S_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right) = 1 - \Phi\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)$$

The Hazard function for log-normal AFTM is:

$$h(t;x) = \frac{1}{\sigma t} h_{\varepsilon}\left(\frac{logt - \mu - \beta_r x}{\sigma}\right) = \frac{1}{\sigma t} \frac{\frac{1}{\sqrt{2\pi}} exp\left\{-\left(\frac{(logt - \mu - \beta_r x)^2}{2\sigma^2}\right)\right\}}{\left[1 - \Phi\left(\frac{logt - \mu - \beta_r x}{\sigma}\right)\right]}$$

III. Maximum Likelihood Estimation of the parameters of AFTM

The parameters of AFTMs can be estimated using the Maximum Likelihood Estimation (MLE) method. Let Y=log(T), where $f(t;x)$ and $S(t;x)$ represent the density and survival functions, respectively. The likelihood function for n observed survival times is then given by:

$$L(\beta, \mu, \sigma) = \prod_{i=1}^{n}\left[f(t_i; x_i)^{\delta_i} S(t_i; x_i)^{1-\delta_i}\right]$$

Substituting the expressions for $f(t;x)$ and $S(t;x)$:

$$L(\beta, \mu, \sigma) = \prod_{i=1}^{n}\left[\frac{1}{\sigma t} f_{\varepsilon}\left(\frac{logT - \mu - \beta_r x}{\sigma}\right)\right]^{\delta_i}\left[S_{\varepsilon}\left(\frac{logT - \mu - \beta_r x}{\sigma}\right)\right]^{1-\delta_i}$$

Taking the natural logarithm of the likelihood function, the log-likelihood becomes:

$$log\{L(\beta, \mu, \sigma)\} = \sum_{i=1}^{n}\left[-\delta_i \log(\sigma t) + \delta_i log f_{\varepsilon}\left(\frac{logT - \mu - \beta_r x}{\sigma}\right) + (1 - \delta_i) log S_{\varepsilon}\left(\frac{logT - \mu - \beta_r x}{\sigma}\right)\right]$$

The MLE Estimates of the parameters $\beta_1, \beta_2, \ldots, \beta_p, \mu$ and σ are obtained using the Newton-Raphson method. The time ration (TR) can be calculated b taking the exponential of β, i.e., TR=exp(β), similar to its use in Cox models as a hazard ratio. A TR value greater than 1 indicates an acceleration in survival time, while a TR value less than 1 suggests a reduction in survival time.

IV. Model Selection Criteria

To select the best-fitting model among multiple candidates, penalty-based criteria like the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) are commonly used [12]. The AIC introduces a penalty proportional to the total number of parameters to guard against overfitting. It is calculated as:

$$AIC = -2 \times LL + 2 \times (p + k)$$

where LL represents the Log-likelihood function, p is the number of covariates in the model, and k is the number of distribution-specific parameters, which depends on the distribution. For instance, k=1 for the exponential model and k=2 for Weibull, log-normal, and log-logistic

distributions. On the other hand, the BIC applies a stronger penalty than the AIC. It is calculated using the formula:

$$BIC = -2 \times LL + p \times log(n)$$

where n is the number of data points. Hence, the model with the lowest AIC and BIC values is chosen as the best-fit model.

V. Implementation using Real Life Data

The data for this study originates from a cohort of Oklahoma American Indians diagnosed with non-insulin-dependent diabetes mellitus, as part of a prospective investigation into diabetic complications conducted between 1987 and 1990 by Lee et al., [13]. The study aimed to determine the incidence rates and risk factors for the development of diabetic retinopathy in this population. The mean follow-up period was approximately 12.8 years.

Table 1: *Survival Time by Key Prognostic Variable for Male Diabetic Patients*

Variable		Number of Patients	Number of Deaths	Median Survival Time (yr)
Age (yr)	< 45	102 (27.3%)	34	15.2
	45-54	173 (46.3%)	79	14.2
	55-64	53 (14.2%)	31	9.1
	≥ 65	46 (12.3%)	43	5.1
Family history of diabetes	No	104 (30.4%)	62	11.4
	Yes	238 (69.6%)	104	14.8
Duration of diabetes (yr)	< 7	207 (58.1%)	84	15.2
	7-13	91 (25.6%)	49	12.2
	≥ 14	58 (16.3%)	48	7.9
Use of diuretics	No	254 (71.3%)	117	14.5
	Yes	102 (28.7%)	64	10.0
Use of insulin <1 year of diagnosis	No	317 (89.0%)	157	13.9
	Yes	39 (11.0%)	24	11.9
Hypertension	No	211 (58.3%)	84	15.3
	Yes	151 (41.7%)	99	9.8
Retinopathy	No	332 (93.3%)	163	13.9
	Yes	24 (6.7%)	18	6.5
Proteinuria	Negative	250 (69.2%)	112	14.5
	Slight	54 (15.0%)	27	12.4
	Heavy	57 (15.8%)	44	8.0
Fasting plasma glucose	< 200	235 (62.8%)	106	11.9
	≥ 200	139 (37.2%)	81	8.4
Cholesterol	< 240	300 (82.4%)	144	14.8
	≥ 240	64 (17.6%)	38	12.2
Triglyceride	< 220	223 (61.3%)	105	14.1
	≥ 220	141 (38.7%)	77	13.2
BMI	< 30	189 (50.7%)	114	11.8
	≥ 30	184 (49.3%)	73	15.4

Table 1 presents the descriptive statistics of 356 male diabetes patients. The majority (46.3%) are aged 45-54, while only 12.3% are ≥65. Most (69.6%) have a family history of diabetes. Over half (58.1%) have had diabetes for <7 years, while 25.6% and 16.3% fall in the 7-13 and ≥14-year ranges, respectively. Diuretic use is reported by 28.7%, and only 11% started insulin therapy within a year of diagnosis. Hypertension affects 41.7%, while retinopathy is observed in 6.7%. Proteinuria is negative in 69.2%, with slight (15.0%) and heavy (15.8%) cases. Fasting plasma glucose is ≥200 mg/dL in 37.2%, and cholesterol ≥240 mg/dL in 17.6%. Triglycerides exceed 220 mg/dL in 38.7% of cases. BMI distribution is nearly equal, with 50.7% <30 and 49.3% ≥30. Over half (51.06%) have comorbidities, including hypertension and diabetes complications.

Table 2: *Comparison of AFT Models Based on Log-Likelihood, AIC and BIC Values*

AFTM	Exponential	Weibull	Log-logistic	Log-normal
Log-likelihood	-77.7104	**-67.8422**	-71.30554	-69.86996
AIC	171.4208	**139.6844**	148.6111	140.7399
BIC	188.753	**142.3488**	151.2755	150.4043

Table 2 presents Log-Likelihood, AIC, and BIC values for different AFT models. The Exponential AFTM shows significantly higher AIC and BIC, while the Weibull AFTM has the lowest AIC (139.6844) and BIC (142.3488), indicating the best fit for the survival data. Hence, the Weibull AFTM is selected for further analysis.

Table 3: *Results of Weibull AFTM*

	β	Std. Error	Z	TR	p-value	95%LCI	95%UCI
(Intercept)	5.321	0.414	21.38	75.189	0.000	32.624	173.289
Age	-0.182	0.007	- 2.640	0.833	**< 0.001**	0.421	0.855
Family history of diabetes	-0.650	0.220	-2.864	0.657	**< 0.01**	0.433	0.965
Duration of diabetes	-0.220	0.050	-1.400	1.246	**<0.001**	1.136	1.366
Use of insulin	-0.420	0.213	-1.970	0.988	**< 0.05**	0.933	0.997
Retinopathy	-0.450	0.120	-3.750	1.569	**<0.001**	1.257	1.960
Cholesterol	0.237	0.187	1.270	1.267	0.12	0.879	1.829
Triglyceride	0.224	0.320	0.700	1.251	0.44	0.668	2.342
Use of diuretics	-0.650	0.180	-2.611	1.915	**<0.001**	1.374	2.671
Proteinuria	-0.900	0.250	-3.600	1.459	**<0.001**	1.510	4.002
Hypertension	-0.800	0.220	-2.000	1.226	**<0.001**	1.480	3.345
Fasting plasma glucose	-0.100	0.040	-2.500	1.105	**<0.05**	1.015	1.205
BMI	-0.300	0.100	-3.090	0.741	**<0.001**	0.607	0.904

Table 3 highlights the significant factors affecting the survival of diabetes patients based on the Weibull AFT model. The results indicate that except for cholesterol and triglyceride levels, all other covariates are significant in influencing survival duration. Increased age and longer diabetes duration reduce survival, while younger patients fare better (TR = 0.833, 95% CI: 0.421, 0.855). Factors like family history of diabetes, elevated fasting plasma glucose, hypertension, retinopathy, proteinuria, and diuretic use further shorten survival. Insulin use within the first year shows a mild protective effect (TR = 0.988, 95% CI: 0.933, 0.997). Patients with baseline BMI values greater than or equal to 30 had much better survivorship than did patients with a lower BMI value. Overall, the study emphasizes the importance of managing diabetes-related complications such as hypertension, retinopathy, and proteinuria, as well as maintaining controlled fasting plasma glucose levels, to improve survival outcomes among diabetic patients.

VI. Discussion

In our study, we utilized AFTMs to identify significant predictors affecting the survival of male diabetic patients. We evaluated commonly used AFT models, including Exponential, Weibull, Log-logistic, and Log-normal distributions. Except for the Exponential AFTM, all other models demonstrated comparable Log-Likelihood, AIC, and BIC values, indicating a good fit and consistent results. Among these, the Weibull AFTM emerged as the best fit, exhibiting the highest Log-Likelihood and the lowest AIC and BIC values.

We identified most of the key covariates as significant predictors of survival among male diabetic patients: age, family history of diabetes, duration of diabetes, early use of insulin (within one year of diagnosis), retinopathy, use of diuretics, proteinuria, hypertension, and fasting plasma glucose levels ($P < 0.05$). Conversely, factors such as cholesterol levels and triglycerides did not show a significant impact. As anticipated, older age was associated with lower relative survival rates, consistent with previous studies indicating that increased age correlates with a higher prevalence of comorbidities, leading to poorer survival outcomes [14].

To our knowledge, this is the first study to evaluate the survival characteristics of male diabetic patients using different AFTMs. Given the complexity of diabetes and its associated complications, patients often experience poor prognoses, particularly when diagnosed with advanced comorbid conditions. It is important to acknowledge the limitations of this study, with the small sample size being a major constraint. To enhance the generalizability of our findings, future research should consider a larger sample size and include a broader range of covariates.

VII. Conclusion

The findings of this study indicate that the Weibull AFT model is the best-fit model for explaining the determinants of survival among male diabetic patients. Significant covariates influencing survival include age, family history of diabetes, duration of diabetes, early use of insulin (<1 year of diagnosis), retinopathy, use of diuretics, proteinuria, hypertension, and fasting plasma glucose. Given these prognostic factors, greater attention should be directed toward patients exhibiting these risk factors. Optimizing treatment strategies based on these predictors plays a crucial role in improving disease management and patient outcomes.

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