Accelerated Failure Time Model with Weighted Least-Squares Estimation: Application on Survival of HIV Positives

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Research

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Accelerated Failure Time Model with Weighted Least-Squares Estimation: Application on Survival of HIV Positives

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Abstract

Background: *Survival analysis is the most appropriate method of analysis for time to event data. The classical accelerated failure time model is a more powerful and interpretable model than the Cox proportional hazards model provided that, model imposed distributional and homoscedasticity assumptions satisfied. However, most of the real data are heteroscedastic which violate the fundamental assumption and consequently, the statistical inference could be erroneous in accelerated failure time modeling. Weighted least squares estimation for accelerated failure time model is an efficient semi-parametric approach for time to event data without the homoscedasticity assumption, which is developed recently and not often utilized for real data analysis. Thus, the study was conducted to ascertain the predictive performance of weighted least squares estimation method over the classical methods.*

Methods: *We analyzed a sample of 203 real Antiretroviral Therapy dataset. We compared the results from clasical methods of estimation for accelerated failure time model with the results revealed from the weighted least squares estimation.*

Results: *We found that the data are heteroscedastic. The weighted least squares estimation revealed more accurate, and efficient estimates of covariates effect. It also detected more significant covariates. Accordingly, survival of HIV positives varies with age, weight, functional status, CD4 percent, and clinical stages.*

Conclusions: *The weighted least squares estimation performed best in predicting the survival of HIV patients. Thus, we recommend future researchers should utilize weighted least squares estimation rather than the classical methods when the homoscedasticity assumption is violated.*

Keywords: Accelerated Failure Time; Classical Estimation; Weighted Least Squares Estimation; Heteroscedasticity; Predictive Performance.

Background

Although the Cox proportional hazards (PH) model (Cox, 1972) is the most employed technique in survival analysis because of its reduced set of assumptions about the baseline hazard function, formulation of the accelerated failure time (AFT) model (Kalbfleisch & Prentice, 1980) allows the derivation of a time ratio, which is more interpretable than a ratio of two hazards (Khanal, et al., 2014). The AFT model doesn't require PH which is seldom met assumption of the Cox PH model (Khanal, et al., 2014). It also encompasses relatively a wide range of survival time distributions and yields more powerful estimates than the Cox PH model provided that, method imposed assumptions satisfied (Collett, 2003). Thus, the AFT model is

more appealing in many ways (Yu, Liu, & Chen, 2018).

Conventionally, the rank (Tsiatis, 1990; Lai & Ying, 1991b, 1992; Robin & Tsiatis, 1992; Ying, 1993; Lin & Ying, 1995; Jin, et al., 2003; Zhou, 2005) and least squares (Buckley & James, 1979; Ritov, 1990; Lai & Ying, 1991a; Jin, et al., 2006) are most often used methods of inference for the AFT model (Yu, Liu, & Chen, 2013). The classical AFT models in general are unified by the adoption of a log-linear representation with a particular survival time distribution for the error term (Collett, 2003). These classical methods impose constant variance (homoscedasticity) assumption and hence, doesn't take heteroscedastic data in to consideration. Consequently, rank or least squares estimation (LSE) based inference for heteroscedastic data is not reliable (Yu, et al., 2013; Yu, et al., 2018). The coverage probabilities of the 95% confidence intervals (CI) of the estimated coefficients are considerably lower than the nominal level 0.95 because of the variance estimates of the parameter estimators are mostly under estimated with the homogeneous assumption of variance. Besides, it results in the loss of efficiency for coefficient estimators. Moreover, the intercept estimation is inconsistent.

To incapacitate these negative aspects, (Yu, et al., 2013) proposed the weighted least squares estimation (WLSE) for the AFT model. It is a semi-parametric approach to handle both homoscedastic and heteroscedastic data beyond incorporation of censorship. Therefore, this article is aimed to formulate a detective model that results in reliable, efficient, and interpretable estimates of the effects of significant covariates on HIV patients' survival. In doing so, we compared the predictive performance of the classical AFT method with WLSE to ascertain the validity, detective ability, and efficiency of inference from WLSE based on real Antiretroviral Therapy (ART) dataset with more covariates.

Data and Research Method

Description of the Dataset

The data was obtained from University of Gondar referral hospital ART database. A sample of 203 HIV patients who started ART between 2003 and 2009 were followed until April, 2015. Among which 17% were with actual death time and the remaining were right censored times.

The response variable was considered to be the length of time measured in months from ART initiation until time of death (censor). There were six covariates recorded at the beginning of ART including age and weight in addition to the covariates in Table 1.

Table 1 : Log-rank Test for Categorical Variables

Covariates	Labels	No. of Patients	No. of Deaths	P-Value
Gender	Female	118	21	1.000
	Male	85	14	1.000
Functional Status (FS)	Working	136	15	0.002
	Ambulatory	55	14	0.002
	Bedridden	12	6	0.002
Clinical Stage (CS)	I, II, & III	154	13	0.000
	IV	49	22	0.000
CD4 Percent	12%-15%	162	33	0.100
	16%-28%	41	2	0.100

Covariates with probability of being significant less than or equal to 10% in the log-rank test were potentially considered for further analysis besides age and weight.

The Classical AFT Model

The AFT model regresses survival time $\mathcal{T}$ on covariates X as follows,

$$T_i \equiv \log(\mathcal{T}_i) = \alpha_0 + \beta_0^T X_i + \in_i,\ i = 1, 2, \ldots, n \qquad \text{Equation 1}$$

Where α_0 is the true intercept and β_0 is the true p-dimensional vector of slope parameters. Let $\tilde{X} = [1\ X]$ and $\tilde{\beta}_0^T = [\alpha_0\ \beta_0^T]$ where $\tilde{\beta}_0$ is the

vector of coefficients for the AFT model (Yu, et al., 2013).

In this model, let $\in_i = \sigma e_i$. Then, e_i is the error term which is independently and identically distributed (IID) with unspecified distribution function F of mean 0 and variance 1. In other words, $\in_i$ IID error term with a constant variance σ^2 (homoscedasticity) assumption and a particular survival time distribution (Yu, et al., 2018). The most commonly used survival distributions for AFT metric are exponential (Exp), weibull (Weib), loglogistic (Logl), lognormal (LN), and generalized gamma (GG) (Khanal, et al., 2014). The exponential distribution is the special case of the weibull distribution. Similarly, the generalized gamma distribution includes a wide range of family distribution as its special case. Its flexible hazard function allows for many possible shapes such as weibull, exponential, and lognormal distributions with various values of the shape and the scale parameters (Collett, 2003). Therefore, we used the GG AFT model for evaluating and selecting an appropriate model from its parametrically nested possible AFT models for the dataset by testing the shape and the scale parameters.

Moreover, we used information criterion statistics (ICS), $-2\log likelihood$ (-2LL) for comparison of the performance of parametrically nested classical AFT models and Akaike information criterion (AIC) for comparison the performance of other alternative classical AFT models. Accordingly, the best model was the one with the smallest ICS indicating the minimum lose of information.

Finally, the performance of the best fitted classical AFT model was compared with the model fitted by the WLSE. This comparison was based on either the magnitude of standard errors (SE) of estimates or the length of confidence intervals to determine accuracy and efficiency of a given inference. Detective capacity was also another interest of comparison

The Weighted Least-Squares Method

The WLSE method frees the homoscedasticity assumption in Equation 1.

Define $Z = \min\{T, C\}$ and $\delta = I(T \le C)$ where, C is the logarithm of the censoring time, T is as defined in Equation 1, $I(\cdot)$ is the indicator function. Then the observations are denoted by $\{Z_i, X_i, \delta_i\}, i = 1,2,\ldots,n$ and C_i is assumed to be independent of the T_i and X_i. The WLSE utilizes a weighted least-squares equation as in (Yu, et al., 2013) with synthetic observations ($T_i^* = Z_i\delta_i + E(T_i \mid T_i > C_i)(1-\delta_i)\ \ i = 1,2,\ldots,n$) weighted by square root of their variances where the variances are estimated via the local polynomial regression. Then the weighted regression according to (Yu, et al., 2013) is as follows.

$$T_{inew}^* = \alpha_0 x_{i0new} + \beta_0^T X_{inew} + e_i,\ i = 1,2,\ldots,n \qquad \text{Equation 2}$$

Where $T_{inew}^* = T^*/\sigma_n(\mu_i)$; $\sigma_n(\mu_i)$ is the non parametric estimator of $\sigma^*(\mu_i)$, the square root of variance of T_i^*; $x_{i0new} = 1/\sigma_n(\mu_i)$; $X_{inew} = X_i/\sigma_n(\mu_i)$; e_i is as defined in Equation 1.

Based on the weighted least squares regression in Equation 2, all $\tilde{\beta}_0$, including α_0, are slope parameters.

Results and Discussions

We began with assessment of the time varying nature of the covariates in Figure 1. We found that the reference line on zero differences fall with in the 95 % confidence intervals except for WHO clinical stages (CS). Thus, no need to doubt time variability of age, weight, functional status (FS), and CD4 percent.

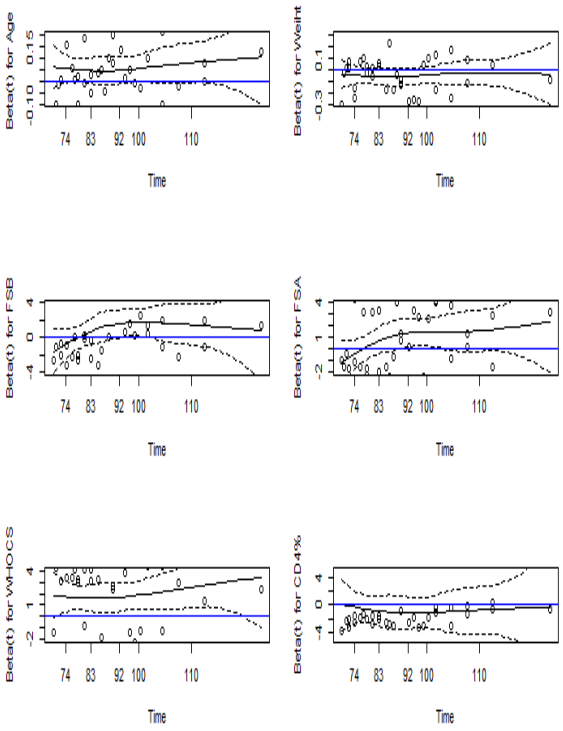

Figure 1 : The Plots of Coefficients over Time

We also examined the plot of the estimated variances versus the means from the weight least squares method, as shown in Figure 2. The data was found to be heteroscedastic.

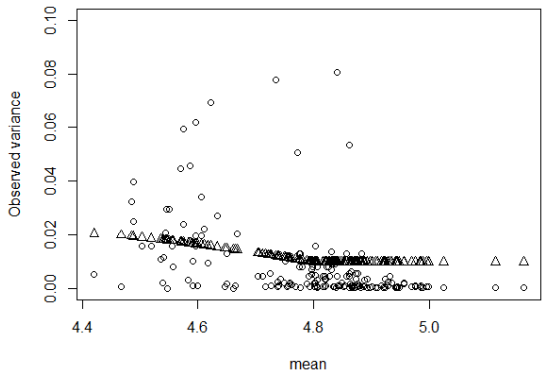

Figure 2 : Variance function estimated from the weighted least squares method. The dots are the observed variances and the triangles are the estimated variances.

According to (Yu, et al., 2013), the WLSE is valid inference in such cases. We summarized the results in Table 2. The reference categories are working for functional status; I, II, & III for clinical stage; and 12%-15% for CD4%. The level of significance is considered to be 5%.

Table 2 : Weighted Least Squares Estimation

Covariates	Estimates	95% CI	
Constant	4.773	4.722	4.824
Age	-0.00516	-0.00518	-0.00514
Weight	0.00497	0.00495	0.00498
BFS	-0.04742	-0.07420	-0.02064
AFS	-0.02048	-0.02721	-0.01374
CS(IV)	-0.25080	-0.25513	-0.24646
CD4%16-28	0.10320	0.01143	0.19496

In addition to the WLSE, we revealed the results from the classical methods namely, parametric AFT model, rank, and least squares estimation (LSE) to ascertain the superiority of WLSE over the classical methods. We selected the appropriate parametric AFT model for the dataset among the exponential, weibull, loglogistic, lognormal, and generalized gamma AFT models.

Table 3 : Estimates of Shape Parameter (Q) from the Generalized Gamma AFT Model.

Estimates	95%CI	
	LL	UL
0.411	-0.507	1.328

The shape parameter (Q) from the classical GG AFT model in Table 3, is not significantly different from 0 or 1. This indicates that the LN and the weibull AFT models are likely to be appropriate among the special cases of GG AFT model. However, Q is estimated to be 0.411 and it is nearer to 0 than to 1. For this reason, we selected the LN AFT model over the weibull. Moreover, we considered ICS in Table 4 for selecting the most appropriate model.

Table 4 : Information Criterion Statistics for Classical AFT Models

ICS	Exp	Weib	Logl	LN	GG

-2LL	479.7	380.6	379.9	379.8	379.2
AIC	485.7	390.6	389.9	389.8	391.2

The smaller magnitude of the information criterion statistics (ICS) for LN AFT model led us to the conclusion that the LN AFT model is the best fit for the data. Therefore, we used the LN AFT model to represent the parametric AFT models for comparison. However, the detective performance of the other parametric AFT models was the same with LN AFT model as in Table 5 except the exponential one in which weight was not significant.

Table 5 :Estimates from the Classical Methods.

Method	Covariates	Estimates	SE	95%CI	
				LCL	UCL
LN AFT	meanlog	4.832	0.1564	4.526	5.139
	sdlog	0.232	0.0286	0.182	0.295
	Age	-0.009	0.0029	-0.015	-0.003
	Weight	0.008	0.0032	0.002	0.014
	CS	-0.278	0.0599	-0.395	-0.160
Rank	Age	-0.009	0.0033	-0.015	-0.002
	Weight	0.008	0.0033	0.001	0.014
	CS	-0.277	0.0572	-0.389	-0.165
LSE	Age	-0.009	0.0027	-0.014	-0.004
	Weight	0.008	0.0026	0.003	0.013
	CS	-0.272	0.0530	-0.376	-0.168

According to the result in Table **5**, the detective performance of the three classical methods was similar in this particular study. Accordingly, age, weight, and WHO clinical stage were significant based on these methods. However, an efficient method is obviously more likely to identify significant covariates. Thus, we found the LSE to be the most efficient among the classical methods in Table 5 since the standard errors (SE) associated with its estimates are relatively small. Similarly, LN AFT model was more efficient as compared to the rank method.

Nevertheless, we compared the predictive performance of LSE with the WLSE since the LSE was the best among the classical methods. The results in Table 2 revealed that the WLSE is more accurate than the LSE. It resulted in efficient estimates of covariates effect on HIV patients' survival since the narrow CI indicates relatively small standard error of estimates. It also identified more significant covariates since functional status and CD4 percent were additional significant covariates which were not identified by LSE. (Yu, et al., 2013) Made the conclusion about validity of inference based on WLSE. Moreover, the WLSE for AFT model depends on synthetic observations based on transformation that allows the same conditional expectations as the logarithm of survival time (Delecroix, et al., 2008). This eases interpretation of the estimates. Therefore, the predictive performance of AFT model based on WLSE is superior to the classical methods. We discussed the results of WLSE as follows.

Holding the effects of all other factors constant, the log survival time for a patient with an additional year of age is 0.00516 less. This indicates that the survival probability of younger patients is better than older. Studies by (Sieleunou, et al., 2009; Ayalew, et al., 2014; Assefa & Wencheko, 2012) confirmed that the hazard of death increases with higher age intervals. These studies also confirmed that less weight, low level of CD4, higher clinical stage, and non-working functional status are associated with increased hazard rate. Similarly, we found that the logarithm of survival is 0.00497 more for a Kg of additional weight. For patients with bedridden and ambulatory functional status, it is respectively 0.047 and 0.0205 less as compared to those with working functional status. Moreover, it is 0.251 less for patients at clinical stage IV than patients at lower stages and it is 0.1032 more for patients with CD4 percent of 16% - 28% as compared to those with lower CD4 percent. In our study, gender of patients was not significantly associated with their survival at 5 %

level of significant. In contrast, it was found to be significant according to the three studies we mentioned in this discussion.

Conclusions and Recommendations

We utilized AFT models based on the classical and WLSE methods on real ART dataset with more covariates than considered in (Yu, et al., 2013). Among possible parametric AFT models, the lognormal AFT model fitted the data well. We compared the results from this model with the results from LSE and rank methods. From the classical methods, LSE was found to be the best; LN AFT the second; and rank the least. Consequently, we compared LSE with WLSE. The WLSE was found to be more efficient than the classical method. It detected more significant covariates. As a result, the WLSE performed best in predicting the survival of HIV patients. However, the data was heteroscedastic. Thus, we recommend future researcher extend the application of WLSE to homoscedastic real dataset with more covariates to ascertain its validity. They should utilize WLSE rather than the classical AFT methods when the homoscedasticity assumption is violated to obtain efficient estimates. Moreover, health workers should be more cautious when a patient is in advanced clinical stages, old in age, relatively lower in weight, in bedridden or ambulatory functional status, or with lower CD4 percent during ART initiation.

List of Abbreviations

AFS: Ambulatory Functional Status; AFT: Accelerated Failure Time; AIC: Akaike Information Criterion; ART: Antiretroviral Therapy; BFS: Bedriden Functional Status; CI: Confidence Intervals; CS: Clinical Stage; EXP: Exponential; FS: Functional Status; GG: Genralized Gamma; ICS: Information Criterion Statistics; IID: Independently and Identically Distributed; Kg: Kilogram; LCL: Lower Confidence Limit; LL: Log Likelyhood; LN: Log-Normal; Logl: Loglogistic; LSE: Least Squares Estimation; PH: Proportional Hazards; SE: Standard Errors; UCL: Upper Confidence Limit; Weib:Weibull; WHO: World Health Organization; WLSE: Weighted Least Squares Estimation

Declarations

Ethics Approval and Concent to Participante

Not Applicable.

Concent for Publication

Not Applicable.

Availability of Data and Material

All data analysed during this study are included in this published article as a supplementary material with the file name “ART Dataset.csv”.

Competing Interests

The authors declare that they have no competing interests.

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Not Applicable.

Authors’ Contributions

Both authors YAM and DGC generated the idea, YAM as a corresponding author analyzed and interpreted the data, DGC contributed as a supervising author. Both authors read and approved the final manuscript.

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Figures

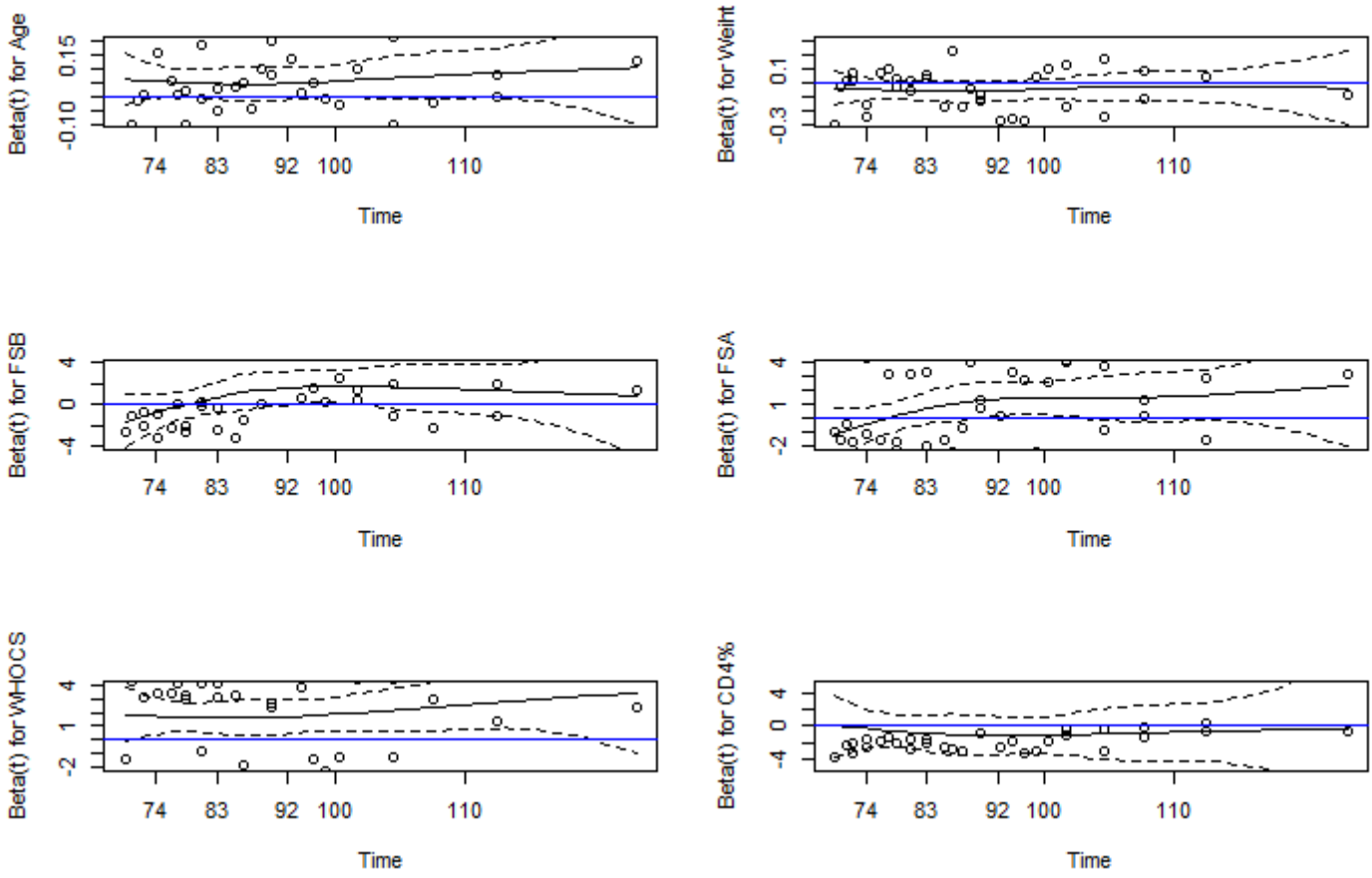

Figure 1

The Plots of Coefficients over Time

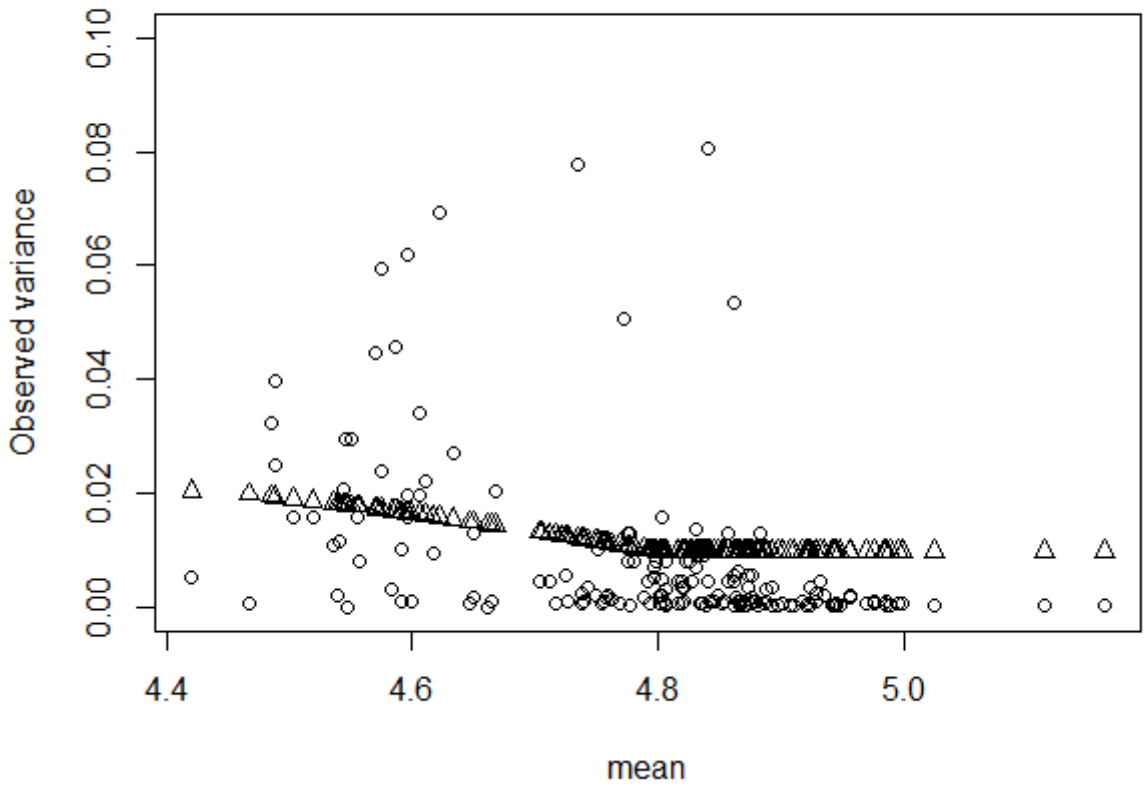

Figure 2

Variance function estimated from the weighted least squares method. The dots are the observed variances and the triangles are the estimated variances.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- ARTDataset.csv