A Comparison between Accelerated Failure-time Model, Kaplan-Meier Survival Model and Cox Proportional Hazard Models in Analyzing the Survival of Chronic Granulomatous Disease

Aboalyem M.[1]
[1]Statistics Department, Faculty of Science, Misurata University
m.aboalyem@misuratau.edu.ly

submittion date: 18-06-2021 acceptance date: 24-06-2021 publishing date: 01-10-2021

Abstract:
Survival analysis is a branch of statistics, which is focused on the analysis of time-to-event data. A primary focus of Survival analysis in medicine is modeling time to surviving a particular disease. In this paper, survival analysis was carried out on Chronic Granulomatous Disease (CGD) data modeling time to surviving the disease.
The Kaplan-Meier approach was used to describe the survival functions of (CGD) patients and Log-rank tests were used to compare the survival curves among groups. Different kinds of models such as Cox Proportional Hazard Model and Accelerated Failure Time (AFT) models like the Weibull AFT model to be used for modeling the time to surviving from (CGD). Models selection criteria were used as a guide to unravel the best model for modeling (CGD).

Keywords: Kaplan-Meier approach, Cox Proportional Hazard Model, Accelerated Failure Time (AFT) model, Weibull Model.

Introduction

Chronic Granulomatous Disease (CGD) is an inherited primary immunodeficiency disease (PIDD) that increases the body's susceptibility to infections caused by certain bacteria and fungi. Granulomas are masses of immune cells that form at sites of infection or inflammation. People with CGD are unable to fight off common germs and get very sick from infections that would be mild in healthy people. This is because the presence of CGD makes it difficult for cells called neutrophils to produce hydrogen peroxide. The immune system requires hydrogen peroxide to fight specific kinds of bacteria and fungi.
These severe infections can include skin or bone infections and abscesses in internal organs (such as the lungs, liver, or brain). Aside from the defective neutrophil function in CGD, the rest of the immune system is normal. People with CGD can be generally healthy until they become infected with one of these germs. The severity of this infection can lead to prolonged hospitalizations for treatment.
Children with CGD are often healthy at birth but develop severe infections in infancy or early childhood. The most common form of CGD is genetically inherited in an X-linked manner, meaning it only affects boys. There are also autosomal recessive forms of CGD that affect both sexes. Therapeutic options for CGD include prophylactic antibiotics and antifungal medications, interferon-gamma injections, and aggressive management of acute infections. Bone marrow transplantation can cure CGD, however, this therapy is complex and transplant candidates and donors must be carefully selected, weighing the risks and benefits carefully. Researchers are investigating other approaches including gene therapy as a future option. (American Academy of Allergy, Asthma & Immunology).Treatment of patients with CGD with intracellular active antibiotics and additional interferon-gamma as infection prophylaxis does it safely and justified[1].

Material and Methods

In this project, we use real data for 203 eligible patients with CGD that were accrued by the International CGD cooperative Study Group (1991) [2], and we will use three important variables that we think will impact our results. The first variable is Treatment and it has two kinds of treatments, and we give code 1 for the Gamma Interferon, and 2 for placebo and we use this variable to see the interferon-gamma as treatment. The second variable is Age and as we can see from this variable, we have more than half of the patients are children. The last important variable is Gender and we choose this to observe which gender impacts the Gamma Interferon.

The CGD study, which is described in a report by the International CGD Cooperative Study Group (1991), was designed to have a single interim analysis when the follow-up data as of July 15, 1989, were complete. The monitoring committee for the trial terminated the trial at a meeting on September 22, 1989, based on the interim analysis. The treatment given to each patient was unblinded at the first scheduled visit for that patient following the decision of the monitoring committee.

We will use a modified version of the CGD data set (cgdModProject2013.csv) and will only consider the time to the initial infection from study entry until the first scheduled visit of the patient after the decision of the monitoring committee (T1). These infections are those observed through the interim analysis date of record (7/15/89) as well as the additional data on the occurrence of serious infections between the interim analysis cutoff and the final blinded study visit for each patient.

Statistical methods section

1. Accelerated Failure Time (AFT) Models:

AFT models are describe stretching out or contraction of survival time as a function of predictor variables.

One of the common models is **Weibull Model** [3]:

$$\boldsymbol{h(t)} = \boldsymbol{\lambda p t^{p-1}} \quad \textbf{for } 0 < t < \infty, \boldsymbol{\lambda} > 0, p > 0$$

The parameterize $\boldsymbol{\lambda}$ with:

$$\boldsymbol{\lambda} = \boldsymbol{e^{(\beta_0 + \beta_1 Trt)}}$$

Then the hazard ratio (TRT = 1 vs. TRT = 0) is

$$\boldsymbol{HR} = \frac{\boldsymbol{e^{(\beta_0+\beta_1)} p t^{p-1}}}{\boldsymbol{e^{(\beta_0)} p t^{p-1}}} = \boldsymbol{e^{(\beta_1)}}.$$

which indicates that the PH assumption is satisfied.

2. Kaplan-Meier Survival Model:

The Kaplan-Meier curve illustrates the survival function. It's a step function illustrating the cumulative survival probability over time. The curve is horizontal over periods where no event occurs, then drops vertically corresponding to a change in the survival function at each time an event occurs.

also known as the product limit estimator, is a non-parametric statistic used to estimate the survival function from lifetime data. In medical research, it is often used to measure the fraction of patients living for a certain amount of time after treatment. The estimator is given by:

$$\widehat{S}(t) = \prod_{j=1}^{k}\left(\frac{n_i - d_i}{n_i}\right) \quad [4]$$

One of the most common estimators and known as Greenwood's formula is estimated variance of the estimate:

$$\widehat{Var}(\widehat{S}(t)) = \widehat{S}(t)^2 \Sigma_{t(i)\le t} \frac{d_i}{n_i(n_i - d_i)} \quad [5]$$

where d_i is the number of failures (deaths) and n_i represent the number of people who survive to $t(i)$, (this is the number in the risk set at $t(i)$) , for $t(i) \le t$.

3. Cox proportional hazards (PH) Model:

A popular model used in survival analysis that can be used to assess the importance of various covariates in the survival times of individuals or objects through the hazard function. In addition, the quantitative impact of these variables on important lifetime variables of interest (such as median survival) can be described and it follows up:

$$log\ h\ (t|X) = log\ h_0(t) + \beta X = \alpha(t) + \beta X$$

$$S(t\backslash X) = \{S_0(t)\}^{e^{(\beta x)}}$$

$$HR = \frac{h\left(t|X_{1,2,\ldots}\right)}{h\ (t|X_0)} = e^{(\beta x)} = e^{(\beta_1 x_1 + \cdots + \beta_k x_k)}$$

Where X is observe covariates.

This model shows that the hazard ratio is $e^{(\beta_1)}$, and remains constant over time t (hence the name proportional hazards regression). The β values are the regression coefficients that are estimated from the model, and represent the log (Hazard Ratio) for each unit increase in the corresponding predictor variable. The interpretation of the hazards ratio depends on the measurement scale of the predictor variable, but in simple terms, a positive coefficient indicates worse survival and a negative coefficient indicates better survival for the variable in question.

The exact method, assumes the tied results are stemming from imprecise time measurements and calculates the likelihood using all of the possible orderings of the tied data. The exact method will give the "best" estimates for the effects of the covariates, but the computational time can be long. For relatively small datasets, however, this increase in computing time is relatively trivial.

$coef

	Estimate	SE
lambda	3.828e-15	8.647e-15
gamma	5.697e+00	3.857e-01
Gender	1.440e-01	2.267e-01

$HR

	HR	LB	UB
Gender	**1.1549**	0.7406	1.801

$$l_p(\boldsymbol{\beta}, \boldsymbol{X}) = \prod_{i=1} \frac{\prod_{j \in D(ti)} \boldsymbol{\phi_j}}{\boldsymbol{\Sigma}_{q \in \varphi} \boldsymbol{\Phi_q}}$$

Assessing the Fit of the Cox Model:
Martingale residuals are defined for the $\boldsymbol{i\_th}$ individual as:

$$\boldsymbol{M_i = \delta_i - \widehat{\Lambda_i}(X_i)}$$

When the residual $\boldsymbol{M_i}$ can be viewed as the difference between the observed number of deaths (1 or 2) for subject $\boldsymbol{i}$ between time 0 and $\boldsymbol{X_i}$, and the expected numbers based on the fitted model [6].

$coef

	Estimate	SE
lambda	4.071e-15	9.176e-15
gamma	5.700e+00	3.860e-01
Age	6.419e-03	9.6266e-03

$HR

	HR	LB	UB
Age	**1.006**	0.987	1.025

$coef

	Estimate	SE
lambda	3.897e-15	8.938e-15
gamma	5.711e+00	3.873e-01
Treatment	4.947e-02	1.779e-01

$HR

	HR	LB	UB
Treatment	**1.050**	0.7413	1.489

RESULTS AND DISCUSSION

1. AFT Models:

We fitted AFT for all three variables to see the hazard ratio HR and compared with HR in Kaplan-Meier Survival Model.Also we find HR's for (Treatment=1.05, Age= 1.01, and Gender=1.15). Since all of hazard ratios greater than 1 that means the exposure harmful to survival.

2. Kaplan-Meier Survival Model:

From both tables on below, we can see the survival function and stander error for the treatments.

```
> summary(fitkp1)
Call: survfit(formula = Surv(T1, D) ~ Treatment, conf.type = "log-log")
```

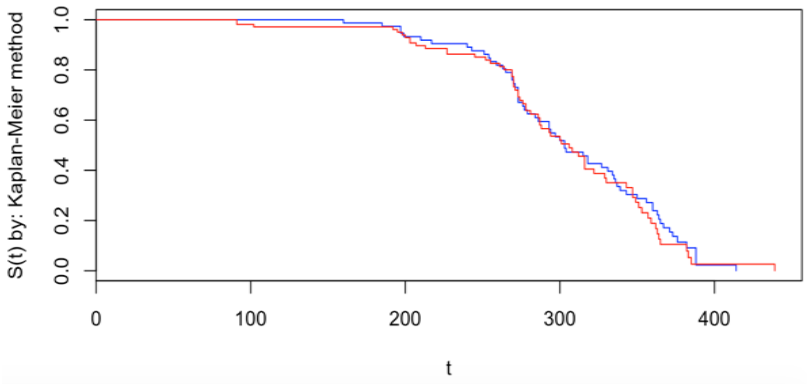
Treatment=1

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
160	77	1	0.9870	0.0129	0.91137	0.998
185	74	1	0.9737	0.0184	0.89880	0.993
197	71	2	0.9462	0.0262	0.86302	0.979
199	69	1	0.9325	0.0292	0.84541	0.971
210	67	1	0.9186	0.0319	0.82770	0.963
217	66	1	0.9047	0.0343	0.81036	0.953
240	64	1	0.8906	0.0366	0.79293	0.944
243	62	1	0.8762	0.0387	0.77541	0.934
251	61	1	0.8618	0.0406	0.75821	0.923
254	60	1	0.8475	0.0424	0.74129	0.913
255	59	1	0.8331	0.0441	0.72461	0.902
259	58	1	0.8187	0.0456	0.70814	0.891
263	57	1	0.8044	0.0470	0.69187	0.879
265	56	1	0.7900	0.0483	0.67579	0.868
269	53	2	0.7602	0.0509	0.64253	0.844
270	51	1	0.7453	0.0520	0.62618	0.831
271	50	1	0.7304	0.0531	0.60999	0.819
273	49	4	0.6708	0.0565	0.54677	0.768
276	44	1	0.6555	0.0572	0.53085	0.755
277	43	1	0.6403	0.0579	0.51508	0.741
279	42	1	0.6250	0.0585	0.49944	0.728
284	41	1	0.6098	0.0590	0.48394	0.714
286	40	1	0.5945	0.0595	0.46856	0.700
293	39	2	0.5641	0.0602	0.43818	0.672

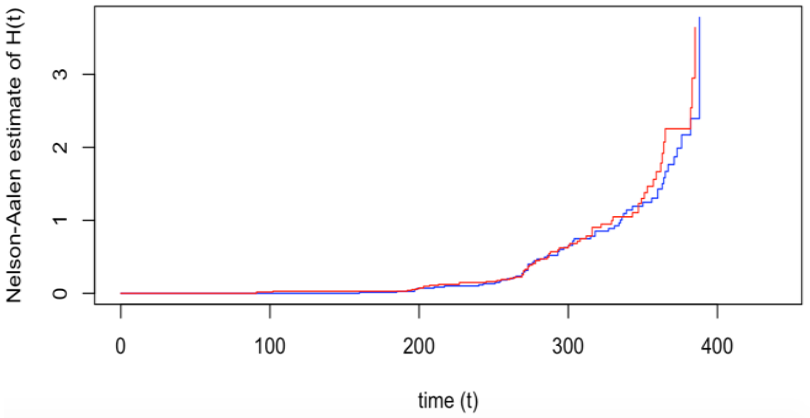
Treatment=2

time	n.risk	n.event	survival	std.err	lower 95% CI	upper 95% CI
91	106	2	0.9811	0.0132	0.92666	0.995
102	102	1	0.9715	0.0162	0.91428	0.991
192	91	1	0.9608	0.0192	0.89884	0.985
195	90	1	0.9502	0.0218	0.88417	0.979
198	89	1	0.9395	0.0240	0.87000	0.972
200	88	1	0.9288	0.0260	0.85620	0.965
203	87	2	0.9075	0.0295	0.82944	0.951
207	83	1	0.8965	0.0311	0.81593	0.943
213	81	1	0.8855	0.0326	0.80240	0.935
227	78	2	0.8628	0.0355	0.77498	0.918
245	74	1	0.8511	0.0369	0.76106	0.909
252	69	1	0.8388	0.0384	0.74622	0.900
255	67	1	0.8262	0.0398	0.73132	0.890
261	64	1	0.8133	0.0412	0.71601	0.880
264	63	1	0.8004	0.0425	0.70093	0.870
269	60	2	0.7737	0.0451	0.67005	0.848
270	57	3	0.7330	0.0485	0.62414	0.815
271	54	1	0.7194	0.0494	0.60918	0.804
273	53	2	0.6923	0.0512	0.57971	0.780
274	51	1	0.6787	0.0519	0.56518	0.769
276	50	1	0.6651	0.0526	0.55077	0.757
278	49	2	0.6380	0.0539	0.52232	0.733
281	45	1	0.6238	0.0545	0.50746	0.720
286	43	1	0.6093	0.0551	0.49230	0.707
287	42	2	0.5803	0.0562	0.46240	0.681
288	40	1	0.5658	0.0566	0.44765	0.668

From figure(1), we can see the survival curve for both treatments is difficult and in figure(2), this is the hazard ratio for treatments by Nelson-Aalen estimation.



Fig(1) survival curve for treatments



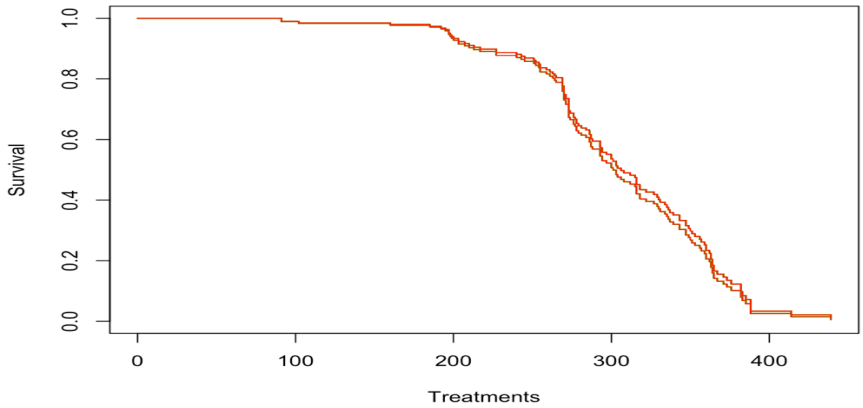
Fig(2) hazard ratio for treatments by Nelson-Aalen estimation

Based on Log-Rank test, the p-value= 0.62 that is mean $h1(t) = h2(t)\ for\ all\ t$. Hence, we can say that there is no significant difference between the two groups regarding the survival.

3. Cox proportional hazards (PH) Model:

Main effects:

After we fitted all variables by exact method, we find the hazard ratio for treatments is 1.09, Age is 1.01, and Gender is 1.16. From this outputs, we can see that the hazard ratio for a one-unit increase in Treatment is 1.09, with 95% confidence interval (0.77,0.1.57), and that the hazard ratio for a one-unit increase in Age is 1.01, with 95% confidence interval (0.99,1.03). Given a hazard ratio of 1.16 from the fitted model, the Cox proportional hazard model states that with each unit increase in Gender, the hazard (h) will decrease from h to 1. 16h.The covariate z is a continuous variable.

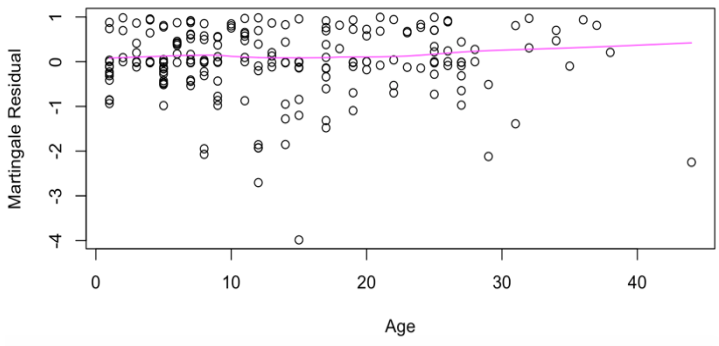


Fig(3) survival curve for treatments by Cox proportional hazard model

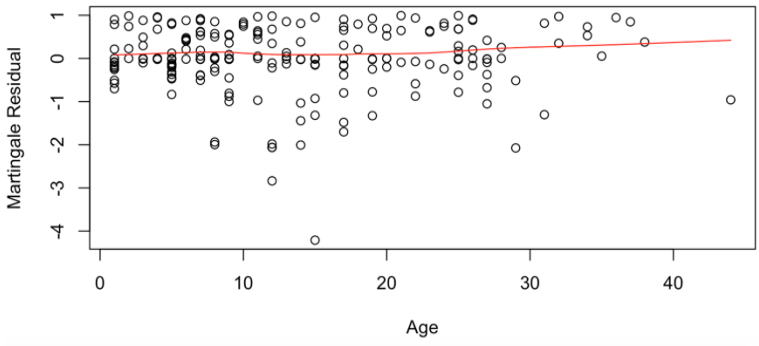
Interaction effects:
We fitted the interaction between the Treatment and the Gender and we found there is significant level between them. On the other hand, we found no significant level between the treatment and the age.

Stratifications:
We fitted the stratification model for (Treatment Age) and (Treatment Gender), and we used the cox.zph command to compare them with the models without the stratification. Hence, the p-value for (Treatment Age) and (Treatment Gender) are not significant too but its kind better than in the first model without the stratification.

Assessing the Fit of the Cox Model "Martingale Residual":
For diagnostic model we use Martingale Residual and we make compare between the model with quadratic term of Age and other model without the transformation for "Age".



Fig(4) Without transformations



Fig(5) With transformations

Conclusion

In conclusion, we fitted some of the models "parametric and non-parametric", and we can see clearly from the results there are slight differences between the hazard ratios for Weibull AFT Models and Cox Models, then we say that data may be fit-with Weibull distribution. After that, we did Kaplan-Meier Survival Model and we found the survival curve for both treatments is not smoother. Also for the Gender variable, we found the hazard ratio going from a male (baseline) to female results in approximately ~70% reduction in hazard. You could also flip the sign on the coef column, and take exp(0.153), which you can interpret as being male resulting in a 1.17 increase in hazard, or that males die ad approximately 1.17x the rate per unit time as females (females die at 1.16x the rate per unit time as males).
In addition, based on the output from the interaction between (treatment *age), we conclude there is a strong association with longer survival times.

REFERENCES

1) Weening RS, Leitz GJ, Seger RA. Recombinant human interferon-gamma in patients with chronic granulomatous disease--European follow up study. Eur J Pediatr. 1995 Apr;154(4):295-8. doi: 10.1007/BF01957365. PMID: 7607280.

2) Muhammad Soomar S. A Secondary Data Analysis on Effectiveness of Gamma Interferon Therapy in Chronic Granulomatous Disease (CGD) Patients Using a Randomized Controlled Trial Data. Austin J Public Health Epidemiol. 2020; 7(1): 1091

3) Zhongheng Zhang, Ann Transl Med. 2016 Dec; 4(24): 484. doi: 10.21037/atm.2016.08.45

4) David Collett, Alan Kimber.(2013).Modelling Survival Data in Medical Research, Third Edition.pp(22).
5) David Collett, Alan Kimber.(2013).Modelling Survival Data in Medical Research, Third Edition.pp(27).
6) Frank E. Harrell, Jr. (auth.). (2015). Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis, second edition.pp(475)

مقارنة بين نموذج وقت الفشل المعجل، ونموذج بقاء كابلان ـ مير ونماذج الخطر التناسبي في تحليل بقاء مرض الغدد التناسلية المزمن

مصطفى أبوعليم[1]
[1]قسم الإحصاء، كلية العلوم، جامعة مصراتة
m.aboalyem@misuratau.edu.ly

الخلاصة:
وتحليل البقاء هو فرع من فروع علم الإحصاء، والذي يركز على تحليل البيانات تدعى time-to-event التركيز الرئيسي لتحليل البقاء على قيد الحياة في الطب هو نمذجة الوقت للنجاة من مرض معين. في هذه الورقة، تم إجراء تحليل للبقاء على قيد الحياة بشأن بيانات مرض الغدد التناسلية المزمن (CGD) التي تحدد الوقت اللازم للنجاة من المرض.
وقد تم استخدم نموذج كابلان-مبير لوصف وظائف البقاء على قيد الحياة لمرضى (CGD) واستخدمت اختبارات Log-rank لمقارنة منحنيات البقاء على قيد الحياة بين المجموعات. إن أنواعاً مختلفة من النماذج مثل نموذج الخطر التناسبي ونماذج زمن الفشل المعجل مثل نموذج Weibull AFT سوف تستخدم لنمذجة الوقت اللازم للبقاء على قيد الحياة من مرضى (CGD)ولقد استخدمت معايير اختيار النماذج كدليل لكشف أفضل نموذج للنمذجة.