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Research Article

EXPONENTIATED GAMMA DISTRIBUTION ON PATIENTS WINDOW PERIOD IN CLINICAL TRIALS

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Abstract

Patients window period in clinical studies is the time between exposure to a disease and the point when a test can detect the disease. The study was conducted at Komfo Anokye Teaching Hospital where 204 patients were followed after reporting for stroke treatment. For comprehensive analysis and estimation of parameters, individual patient's different exposure time until the disease detection were allowed to begin at a common starting window period (w). The data was extracted through exponential plotting fitting points and the result revealed that the was not perfectly followed exponential distribution but rather it was fitted to Gamma Distribution. Patients who reported for treatment at Komfo-Anokye Teaching Hospital have a guarantee time of 1.519 months to 1.608 months without failure.

Keywords: Patients window period, time, stroke, survival function, maximum Likelihood, Estimates

INTRODUCTION

Acute stroke is a medical and surgical emergency, with the outcome of care closely related to time to treatment. The period from the onset of stroke to the start of treatment is defined as "time window". Patients with acute stroke should be admitted to the hospital as soon as possible, and receive thrombolytic therapy within 1 hour of admission according to the National Institute of Neurological Disorders and Stroke (NINDS) standards,1 yet substantial efforts are still needed to understand and minimize both prehospital delays and in-hospital delays.2 However, most healthcare providers have difficulties in achieving the NINDS standards, particularly in developing countries.3 Even in developed countries, only 20.0–35.8% of patients were admitted within the time window for stroke management and prehospital delays are more severe than in-hospital delays. Nevertheless, studies have shown that thrombolytic therapy for patients with acute stroke is not always delivered in time. The stroke chain of survival highlights a timely administration of thrombolytic therapy after patients arrive at the hospital. As the main decision makers in the emergency care of stroke, physicians should have adequate capacity to recognize and treat stroke accurately and promptly within the beneficial "time window". Therefore, it is important to understand physicians' knowledge of and attitudes towards thrombolytic therapy to optimize the use of the therapy. The community healthcare practitioners (CHPs) who deliver frontline care in the health system play an important role in stroke management. Since the launch of a comprehensive health care reform in 2009, the Ghana government has established a strengthened primary care system covering both urban and rural areas. The three-tier health system is underpinned by the community-level primary care institutions who provide diagnosis, initial treatment, and triage for acute and chronic medical care coordinated with secondary and tertiary hospitals. The Ghanaian government has also built a community health service (CHS) infrastructure which allows access to primary care within a 15-minute walking distance in most communities. Therefore, the CHPs are positioned as residents' health gatekeepers, who mainly provide health care services in community health centers (CHCs). Moreover, in the context of the nationwide delivery of the basic public health service package, the CHPs are responsible for managing chronic conditions including hypertension and diabetes. They are also encouraged to attend a variety of continuing medical education and specialized training seminars to enhance the interface between general practice (GP) and specialist care. Given that the GP practitioners have been engaged in a gatekeeping role, the ability of CHPs to recognize stroke onset as early as possible and further manage the referral via green channel to emergency department at the superior hospital becomes critical. We therefore aimed to evaluate knowledge of time window for stroke management among CHPs in primary care and explore factors associated with the awareness of "time window"

METHOD

Patients who die before the study commences are said to be left censored, for this reason their information cannot be tracked. If patients are given a common starting point, their survival times generates a guarantee time for all of them. This guarantee time is known as patient's window period. Window period is a period in which no death occurs until the first failure. For this reason, it is the period between the common starting point for all the patients and the point in time the first failure occurs. Let us denote this period by W, it is practical to subtract W from individual survival times of all the patients. For this reason, the probability density function is given by

$$q(t) = \lambda e^{-\lambda(t-W)}$$

and the survival function is

$$Q(t) = P[T > t] = e^{-\lambda(t-W)}$$

If $t_1 \leq t_2 \leq t_3 \leq \ . \ . \ . t_r$ are the order statistics for the failure times, then the likelihood for the joint distribution is

$$f(t) = \frac{n!}{(n-r)!} \lambda^r e^{-\lambda[\sum_{i=1}^{r} t_i - W]} e^{-\lambda[\sum_{i=1}^{r+1} S_i - W]^{n-r}}$$

$$f(t) = \frac{n!}{(n-r)!} \lambda^r e^{-\lambda V}$$

But V = $\sum_{i=1}^{r} t_i - W] + n - r[\sum_{i=1}^{r+1} S_i - W]$

This is in line with optimization approach but W unit has been subtracted from each observation. Using recursive interval, the time between zero and W is disregarded and W is taken as the point of origin of the patients' survival times

$$\pi_1 = n(t_1 - W)$$

$$\pi_2 = (n-1)(t_2 - t_1)$$

$$\vdots$$

$$\pi_r = (n-r+1)(t_r - t_{r-1})$$

The W's will be cancelled out at all the intervals except the π_1.

$$\sum_{i=1}^{r} \pi_i = \sum_{i=1}^{r} t_1 + (n-r)t_r - nW$$

$$f(\pi) = \sum_{i=1}^{r} \lambda e^{-\lambda\pi_i} = \lambda e^{-\lambda\pi_i} = \lambda^{(r-1)} e^{-\lambda \sum_{i=2}^{r} \pi_i}$$

Let us denote $V^* = \sum_{i=2}^{r} \pi_i$

$$f(V^*) = \frac{(\lambda V^*)^{r-2} \lambda e^{-\lambda V^*}}{\Gamma(r-1)}$$

$f(\pi_1)$ is the only part of the expression that contain W and this based on the smallest observation, that is t_1.

For this reason, the sufficient statistics for (W, λ) are (t_1, and $\sum_{i=2}^{r} \pi_i$)

E(t)= $W + \frac{1}{\lambda}$ and Var (T)= $\frac{1}{\lambda^2}$, hence E(t_1)= $W + \frac{1}{n\lambda}$, and Var (t_1)= $\frac{1}{n\lambda^2}$

The maximum likelihood estimate for the window period W is $f(\pi_1) = \lambda e^{-\lambda n(t_1 - W)} d\pi$

Since the window period ends at the first failure time of the patients, W = t_1, this gives the maximum likelihood of W to be t_1.

To estimate the maximum likelihood estimate for λ: the hazard stroke rate, suppose $f(\pi) = \lambda^r e^{-\lambda V^*}$

$\log f(\pi) = r log\lambda - \lambda V^* + C$, $\frac{d\log f(\pi)}{d\lambda} = \frac{r}{\lambda} - V^*$

Setting $\frac{d\log f(\pi)}{d\lambda} = 0$, $\hat{\lambda} = \frac{r}{V^*}$, but V^* contain W. Substituting the maximum likelihood estimate of W, which is t_1 in $\frac{r}{\lambda} - V^*$ $\hat{\lambda} = \frac{r}{\sum_{i=1}^{r} (t_i - t_1) + (n-r)(t_r - t_1)}$, it is seen that the term $t_1 - t_1 = 0$ has been added to the estimate.

From analytical point of view, V^* is the sum of independent identical distributed random variable. It is therefore obvious to state that V^* has a gamma distribution with scale parameter $\boldsymbol{\lambda}$ and shape parameter $r - 1$. V^* is independent of t_1 because

$t_1 - t_1 = 0$, but t_1 depends only on π_1. In this case, V^* depends only on π_2, π_3 . . . π_r. For this reason

$\hat{\lambda} = \frac{r-1}{V^*}$, $\hat{\mu} = \frac{V^*}{r-1}$. E($V^*$) $= \frac{r-1}{\lambda} = (r-1)\mu$, E($\hat{\mu}$) $= \mu$

In terms of μ, $\mathrm{E}(t_1) = W + \frac{1}{n\lambda}.\widehat{W} = t_{(1)} - \frac{1}{n}\hat{\mu} = t_{(1)} - \frac{V^*}{n(r-1)}.\ \mathrm{E}(\widehat{W}) = W.$

(W, μ) is an estimate of $(\widetilde{W}, \tilde{\mu})$. This is the minimum variance unbiased estimator. A point estimate for the window period is

$$W = t_{(1)} - \frac{V^*}{n(r-1)}, E(\widetilde{W}) = W.$$

$$Var(\widetilde{W}) = \frac{1}{n\lambda^2} + \frac{Var(V^*)}{n^2(r-1)^2} = \frac{1}{n\lambda^2} + \frac{r-1}{\lambda^2 n^2 (r-1)^2} = \frac{1}{\lambda^2 n^2}(1 + \frac{1}{(r-1)})$$

The confidence interval for W is $t_{(1)}$.

$$f(t_{(1)}) = n\lambda e^{-n\lambda(t_{(1)}-W)},\ \pi_1 = n(t_{(1)} - W)$$

$2\lambda\pi_1$ has a Chi-square distribution with 2 degrees of freedom. But $V^* = \sum_{i=2}^{r}\pi_1$ is independent of π_1 and this follow a gamma distribution with shape parameter $r-1$. For this reason

$\frac{2\lambda\pi_1/2}{2\lambda\frac{\sum_{i=2}^{r}\pi_1}{2(r-1)}} = \frac{X_2^2/2}{X_{2(r-1)}^2/2(r-1)}$ which has F distribution with parameters 2 and 2(r-1). The upper and lower bounds for W, is

$$P\left(F_{1-\alpha} < \frac{n(t_1 - W)}{\tilde{\mu}} < F_\alpha\right) = P\left(\frac{\tilde{\mu}F_{1-\alpha}}{n} - t_1 < -W < \frac{\tilde{\mu}F_\alpha}{n} - t_1\right) = 1 - 2\alpha$$

$$t_1 - \frac{\tilde{\mu}F_\alpha}{n} < W < t_1 - \frac{\tilde{\mu}F_{1-\alpha}}{n}$$

APPLICATION

212 patients with acute stroke data was obtained from the Komfo-Anokye Teaching Hospital in Kumasi, Ghana. Patients times of entry into the hospital for medical checkup were recorded as well as their time of deth (failure), time of absence from the hospital for treatment, time of relocating to a different community. The survival times of patients during data collection were also recorded. The data is made up of 167 censored observations consisting of 80% of the total observation and 45 failure observations representing of 20% of the total observations. The data was arranged in numerical ascendency in an equal interval of t_{i-1} to t_i to ensure that at least every interval has event failure time. This is to avoid truncation of survival times in the intervals. This procedure conforms to the generalized algorithm developed in chapter three. The patients

survival times are arranged from a common start so that patients are assumed to have equal entry time. This removes truncations in the data and put patients event times at equal intervals. Each interval contains an event time, and this makes estimations in the intervals simple. To test, whether the data follows exponential distribution, we used plotting position of the failure times.

Plotting position to test whether the data come from exponential distribution.

A= $(1 - {}^{i}/_{n+1})$ and B = $-\log(1 - {}^{i}/_{n+1})$

Table 1.*Plotting position of the patients failure times*

t_i	Value	A	B	t_i	Value	A	B
1	0	0	0	41	41	0.481	0.318
2	2	0.975	0.0109	42	42	0.468	0.33
3	3	0.962	0.0168	43	43	0.455	0.342
4	4	0.949	0.0227	44	44	0.443	0.354
5	5	0.937	0.0282	45	45	0.43	0.367
6	6	0.925	0.0338	46	46	0.417	0.38
7	7	0.924	0.0343	47	47	0.405	0.393
8	8	0.898	0.0467	48	48	0.392	0.407
9	9	0.886	0.0526	49	49	0.379	0.421
10	10	0.873	0.0589	50	50	0.367	0.435
11	11	0.861	0.0649	51	51	0.354	0.451
12	12	0.848	0.0716	52	52	0.342	0.466
13	13	0.835.	0.0783	53	53	0.329	0.483
14	14	0.823	0.0846	54	54	0.316	0.5
15	15	0.81	0.0915	55	55	0.304	0.517
16	16	0.797	0.0985	56	56	0.291	0.536
17	17	0.785	0.1051	57	57	0.278	0.556

18	18	0.772	0.1124	58	58	0.265	0.577
19	19	0.759	0.1197	59	59	0.253	0.597
20	20	0.747	0.1266	60	60	0.24	0.62
21	21	0.734	0.1343	61	61	0.227	0.644
22	22	0.721	0.1421	62	62	0.215	0.668
23	23	0.708	0.1499	63	63	0.202	0.695
24	24	0.696	0.1574	64	64	0.189	0.724
25	25	0.683	0.1655	65	65	0.177	0.752
26	26	0.67	0.1739	66	66	0.164	0.785
27	27	0.658	0.1817	67	67	0.152	0.818
28	28	0.645	0.1904	68	68	0.139	0.857
29	29	0.633	0.1985	69	69	0.126	0.9
30	30	0.62	0.2076	70	70	0.114	0.943
31	31	0.607	0.2168	71	71	0.101	0.996
32	32	0.595	0.2254	72	72	0.088	1.056
33	33	0.582	0.235	73	73	0.076	1.119
34	34	0.569	0.2448	74	74	0.063	1.201
35	35	0.557	0.2541	75	75	0.05	1.301
36	36	0.544	0.2644	76	76	0.037	1.432
37	37	0.532	0.274	77	77	0.025	1.602
38	38	0.518	0.2856	78	78	0.012	1.921

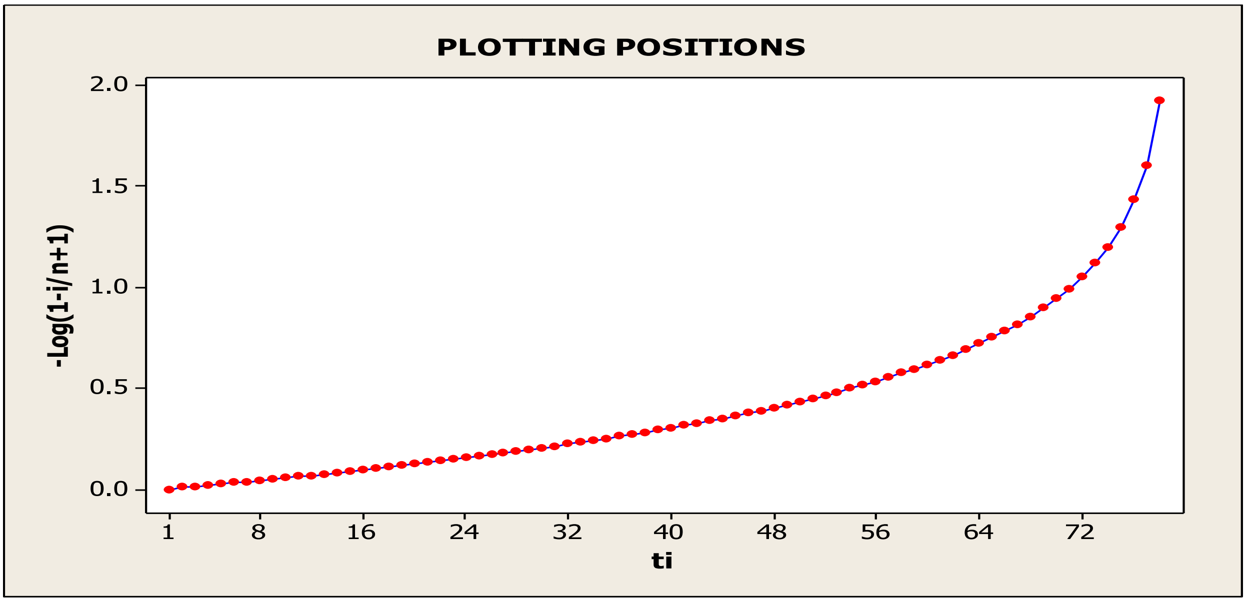

Figure 1: Plotting position of patients' survival event time.

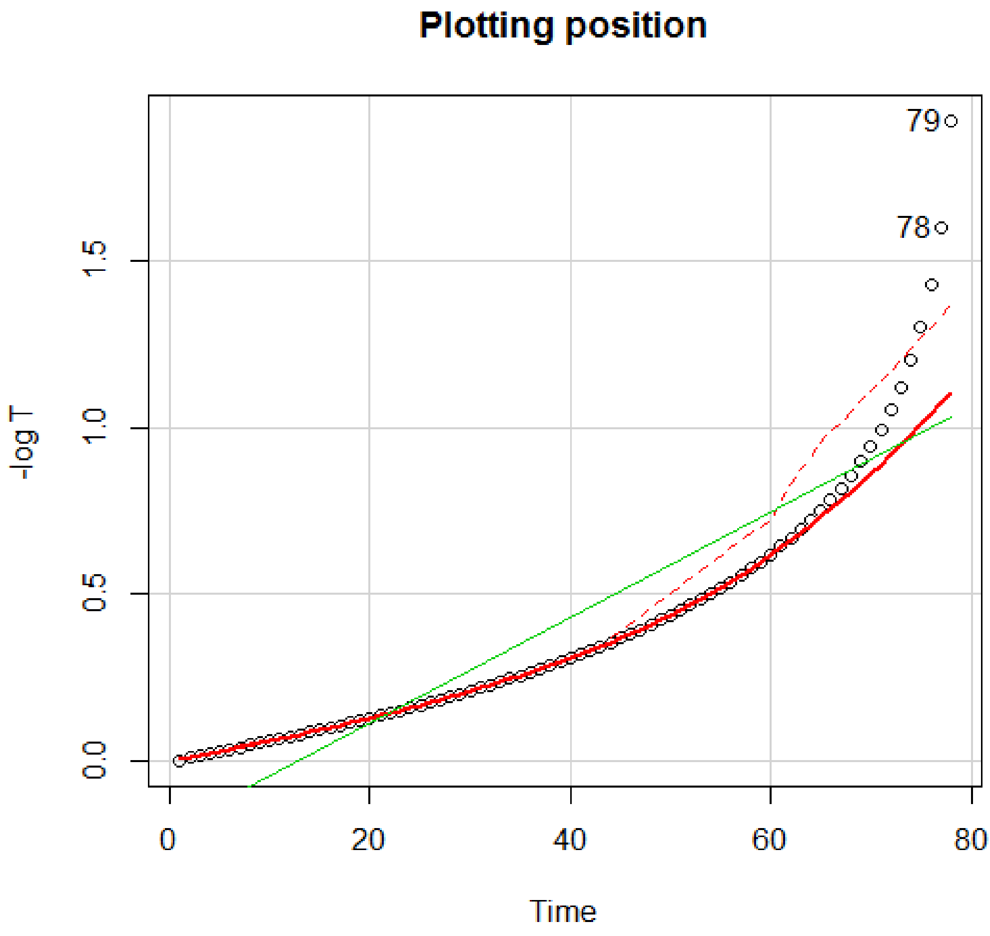

Figure 2: Fitted plotting position of patients' survival event time.

Discussions

Figures 1 and 2 depict the plotting positions of the uncensored values. A plotting position assumed to follow exponential distribution is a straight line. This means that in an exponential distribution, the hazard rate is constant. For this reason, plotting position of data assumed to follow an exponential distribution follow a straight line. Data collected from Komfo Anokye Teaching Hospital does not follow exponential distribution as shown in Figures 1 and 2. The plotting positions may follow complex distribution because the graph has a shape parameter greater than one. For this reason, the assumption of constant hazard rate expected to be seen in the data is violated. From the data,

$$V^* = \sum_{i=2}^{r} \pi_i = 26783 - 33 = 26750$$

This is the total time observed for the patients in two parameters exponential distribution after recording the window period

$r - 1 = 203$ (the total number of failure)

$\hat{\lambda} = \frac{r-1}{V^*} = \frac{203}{26750} = 7.588 \times 10^{-03}$. This is the hazard when using the window period. The variance of the hazard is

$$\text{Var}(\hat{\lambda}) = \frac{\text{r}-1}{\hat{\lambda}^2} = \frac{203}{5.75777\times10^{-05}} = 3525670$$

There is large interval variation of 3525670 risk.

$$\hat{\mu} = \frac{V^*}{r-1} = \frac{26750}{203} = 131.77$$

This is the mean time to death for all patients under the study at known window period.

$$\text{E}(\hat{\mu}) = \mu = 131.77$$

$$\text{E}(V^*) = \frac{r-1}{\lambda} = (r-1)\mu = (203)131.77 = 26749.31$$

In terms of μ,

$$\mathrm{E}(t_1) = W + \frac{1}{n\lambda}. = W + \frac{1}{1011(7.588\times10^{-03})} = W + \frac{1}{7.671468} = W + 0.130353147$$

$$\widetilde{W} = t_{(1)} - \frac{V^*}{n(r-1)} = t_{(1)} - \frac{1}{n}\hat{\mu} = 2 - \frac{1}{1011}\times 131.77 = 2 - 0.1303363 = 1.869$$

$$\mathrm{E}(\widehat{W}) = 1.869 = W$$

$$.\mathrm{E}(t_1) = W + \frac{1}{n\lambda}. = 1.869 + 0.130353147 = 1.999\ .$$

$$Var(\widetilde{W}) = \frac{1}{n\lambda^2} + \frac{Var(V^*)}{n^2(r-1)^2} = \frac{1}{n\lambda^2} + \frac{r-1}{\lambda^2 n^2 (r-1)^2} = \frac{1}{\lambda^2 n^2}(1 + \frac{1}{(r-1)}) = \frac{1}{58.85}(1.004926) =$$
$$0.017076$$

$$Var(\widetilde{W}) = 0.017076$$

$$P\left(F_{1-\alpha} < \frac{n(t_1 - W)}{\tilde{\mu}} < F_\alpha\right) = P\left(\frac{\tilde{\mu}F_{1-\alpha}}{n} - t_1 < -W < \frac{\tilde{\mu}F_\alpha}{n} - t_1\right) = 1 - 2\alpha$$

A two sided $(1-2\alpha)100$ percent confidence interval for W is

$$t_1 - \frac{\tilde{\mu}F_\alpha}{n} > W > t_1 - \frac{\tilde{\mu}F_{1-\alpha}}{n}$$

$$1.999 - \frac{131.77(3.00)}{1011} > W > 1.999 - \frac{131.77(3.69)}{1011}$$

$$1.999 - \frac{395.31}{1011} > W > 1.999 - \frac{486.23}{1011}$$

$$1.999 - 0.391 > W > 1.999 - 0.480 = (1.608 > W > 1.519)$$

patients who reported for treatment at Komfo-Anokye Teaching Hospital have a guarantee time of 1.519 months to 1.608 months without failure.

It should be noted that, the upper bound of the confidence interval is even less than t_1. This is sensible since the probability density function shows that, no failure even occurs before period W.

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