Journal of Fundamental and Applied Sciences

Research Article

ISSN 1112-9867

Special Issue

Available online at http://www.jfas.info

MULTI-SAMPLE NONPARAMETRIC TREATMENTS COMPARISON IN MEDICAL FOLLOW-UP STUDY WITH UNEQUAL OBSERVATION PROCESSES THROUGH SIMULATION AND BLADDER TUMOUR CASE STUDY

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Published online: 10 November 2017

ABSTRACT

In medical follow-up study, the diseases recurrent processes evolved in continuous time and the patients are usually monitor at distinct and different intervals. Therefore, most of the existing methods that assumed identical observation processes might provide misleading results in this case. To address this, a nonparametric test based on integrated weighted different between the mean cumulative functions which characterized both the recurrent processes and observation processes with condition on treatment is proposed to allow unequal observation processes. The empirical power of the proposed test has been investigated via Monte Carlo simulation study and bladder tumour case study. The results arein line with earlier research; the proposed test procedure works well for practical situations and had a good power in detecting treatment difference.

Keywords: nonparametric; unequal observation; multi-sample; treatments comparison.

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doi: http://dx.doi.org/10.4314/jfas.v9i6s.13

1. INTRODUCTION

In medical follow-up study, patients are usually observed at several irregular time points, the actual time of diseases occurrences are unknown and only the number of occurrences between subsequence follow-up is recorded. These data are known as panel count data [11]. The example of panel count datathat given in this paper arising from bladder tumours study conducted by the Veterans Administration Cooperative Urological Research Group [4]. All patients had superficial bladder tumours history, the tumours were removed and patients were randomized to one of the three treatments, placebo, thiotepa or pyridoxine. These patients experienced several recurrences during the follow-up study. The number of new tumours discovered at each follow-up was recorded and were removed at clinical visits. Furthermore, the number of clinical visit and the observation times are varying across the patients. The main interest in this paper is to compare the effectiveness of different treatments in medical follow-up studies that account for unequal observation processes.

In medical, the diseases recurrent processes evolved in continuous time and the patients are often monitor at distinct time and different time intervals. In other words, the observation processes are not identical distributed. Most of the existing methods assumed that the observation processes for the patients in different treatment groups are identical distributed [2], [3, 8-9, 16, 20]. There exist limited literatures for nonparametric comparison, which consider unequal observation processes between treatments [7, 12, 19].As medical follow-up data involves more than one observation time point for each subject that may vary across subject and the number of subject in each treatment groups may vary across treatments, the existing methods which assume identical observation processes may not be feasible in practice. To address this, a multi-sample distribution free test based on the integrated weighted different between mean cumulative functions that characterized the recurrences and observation processes with condition on treatment group is present in this paper.

2. FORMULATION

2.1. Basic Notation

Consider k+1 different treatment groups of independent subjects in a recurrent event study with total sample size n. Suppose only panel count data are available and observation

processes are different for the subjects from different groups. Let n_l denote the number of subjects in the lth group and $s_l$the set of indices for subjects in group l where $n_1 + n_2 + \ldots + n_{k+1} = n$. Also let $N_{il}(t)$ denote the counting process of the total number of recurrent event occurrences up to time t from subject i in lth group with $\Lambda_l(t;Z_i) = E[N_{il}(t)|Z_i]$ the marginal expected number of recurrent events up to t of $N_{il}(t)$ given Z_i for i in s_l,l = 1, … , k + 1 and Z_i is a group-indicator associated with subject i.

For panel count data, each subject is observed only at discrete time points where the ordered distinct observation time points for subject i is denote by $T_{i,1} < T_{i,2} < \ldots < T_{i,mj}$, j = 1, 2, … ,$m_i$ with m_i representing the total number of observation time points for subject i. Let C_i denote the censoring or follow-up time of subject i and τ be the longest follow-up time of all subjects in the study. The observed data are taken to be independent and identical copies of $D_i$where the observation data consist of $D_i = \{N_i, Z_i, C_i, T_{ij}, m_j\}$ and are independent of the counting process N_i's.The union of all distinct observation time points denote by$t_1, t_2, \ldots, t_m$and the censoring times for subject iis the last observation time point for subject i in [0, τ].

2.2. The Observation Processes

Fig. 1 displays the distribution of the clinical visits for placebo treatment and thiotepa treatment in bladder tumour case study. It appears that the patients in the thiotepa group have more follow-up as compared to the patients treated with placebo treatment. The observation processes between placebo treatment and thiotepa treatment are not identical distributed in this case.

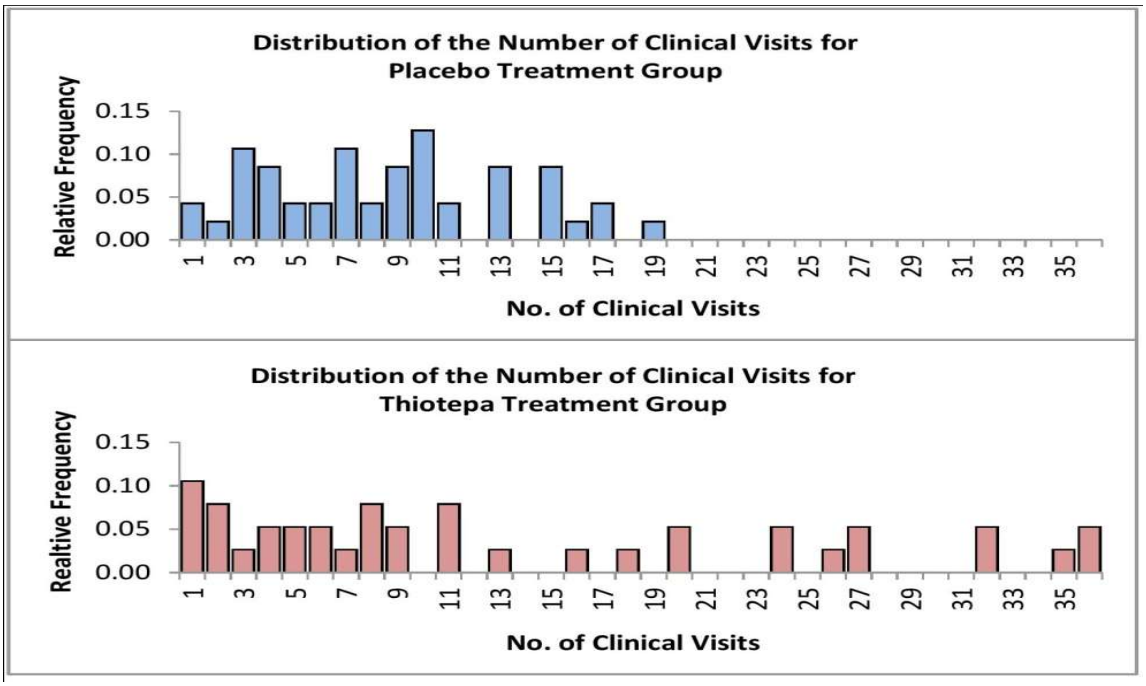

Fig.1. Distribution of clinical visits for Placebo treatment and Thiotepa treatment

To deal with the unequal observation processes between treatment groups, the number of observations formulated is proportional between groups as it fit most of the event history analysis. An example from bladder tumour study is shown in Fig. 2.

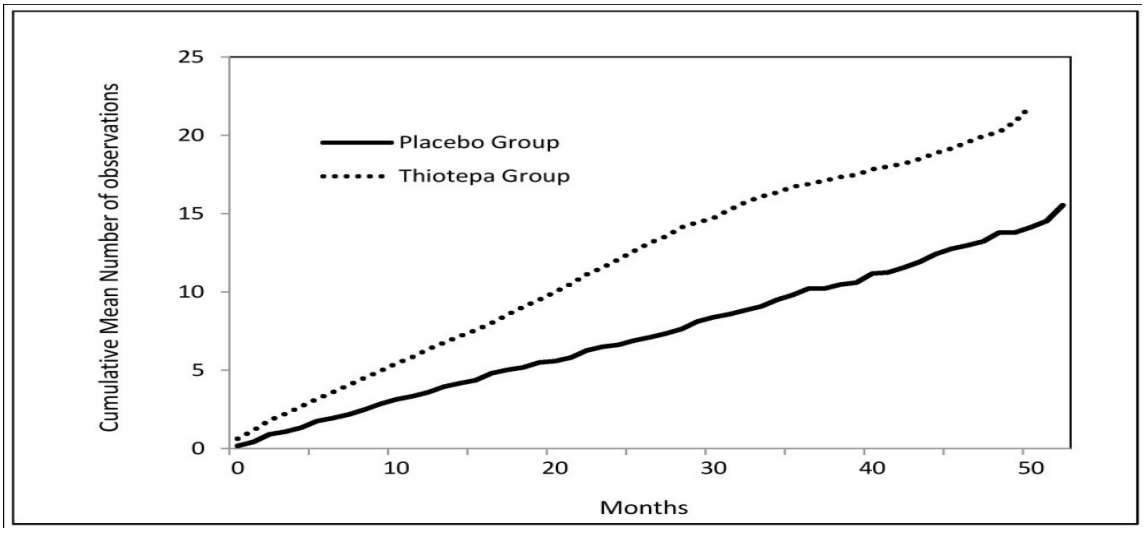

Fig.2. Cumulative number of clinical observations for Placebo treatment and Thiotepa treatment

The total number of observation for subject i is formulated as model in Equation (1).

$$m_i = \exp(\gamma Z_i) \quad (1)$$

where $\gamma = 0$ means the observation processes between two groups are equal and otherwise $\gamma \neq 0$.

2.2. The Recurrence Processes

In order to mimic the situation tested in this paper, the recurrence event, N_{il}'s are assume follow a mixed Poisson processes that result more variability as compared with Poisson processes. The mean recurrence at time t for lth treatment group is the proportion of total number of recurrence observed in lth treatment group at time t over total number of observation at time t.

$$N_l^*(t) = \frac{\sum_{i \in s_l} I(r_i(t) = 1)}{\sum_i I(O_i(t) = 1)} \tag{2}$$

The mean function of recurrent event occurred up to time t from subject i conditioning on treatment group, Z_i has the form of Equation (3) which is similar to the function given in [6].

$$E\left[\int_0^\tau \frac{N_i(t)dN^*}{\exp(\gamma Z_i)} \mid Z_i\right] = \int_0^\tau \mu(t)S(t)\lambda_0(t)dt \tag{3}$$

where $\lambda_0(t)$ is known baseline mean, $\mu(t)$ common mean of $N_i(t)$ and γ is a parameter representing the difference between two groups.

The cumulative meannumber of recurrence for lth treatment group can be written asin Equation (4).

$$\tilde{N}_l(t) = \sum_{i \in s_l} \int_0^\tau \frac{N_i(t)dN^*}{\exp(\gamma Z_i)} \tag{4}$$

The mean cumulative function given treatment group is accumulate of the proportion of the product of total number of patient at risk in lth treatment group and mean tumour recurrenceto the size of the risk set observed at time t_j, $Y(t_j)$ as written in Equation (5).

$$\hat{\Lambda}_l(t; Z_i) = \int_0^t \frac{Y_l(s)d\tilde{N}_l(s)}{Y(s)} \tag{5}$$

where $Y(t_j) = \sum_i I(t_j \leq C_i)$ denote the at risk indicator prior to time t.

2.2. The Test Statistics

The proposed test statistic has the form of integrated weighted different between group-specific mean and the overall mean as given in Equation (6).

$$\phi_l(\hat{\gamma}) = \frac{1}{\sqrt{n}} \sum_{i \in s_l} \left(Z_i - \bar{Z}\right) \int_0^{\tau} W_l(t) d\left\{\hat{\Lambda}_l(t) - \hat{\Lambda}_0(t)\right\} \quad (6)$$

Followed [6-7], γ can be estimated by solving the partial likelihood score in Equation (7)

$$U(\gamma) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \int_0^{\tau} \left\{ Z_i - \frac{S^{(1)}(t;\gamma)}{S^{(2)}(t;\gamma)} \right\} d\tilde{N}_i(t) \quad (7)$$

where

$$S^{(0)}(t,\gamma) = \frac{1}{n} \sum_{i=1}^{n} I(t \le C_i) \exp(\gamma Z_i) \quad (8)$$

and

$$S^{(r)}(t,\gamma) = \frac{\partial S^{(0)}(t,\gamma)}{\partial \gamma^r}. \quad (9)$$

The null hypothesis can be test based on statistics $T^* = \phi(\hat{\gamma}) \mathbf{V}^{-1}(\hat{\gamma}) \phi(\hat{\gamma})'$ the null distribution can be approximate by a chi-square distribution with k degree of freedom. $\phi(\hat{\gamma})$ is given in Equation (10).

$$\phi(\hat{\gamma}) = \sum_l \phi_l(\hat{\gamma}) \quad (10)$$

In [5] showed that $\phi(\hat{\gamma})$ is asymptotically normal with mean 0 and the variance can be consistently estimated by Equation (11).

$$\mathbf{V}(\hat{\gamma}) = \mathbf{H}(\hat{\gamma}) \boldsymbol{\Gamma}(\hat{\gamma}) \mathbf{H}(\hat{\gamma})' \quad (11)$$

where

$$\mathbf{H}(\hat{\gamma}) = \left(\mathbf{I}, \frac{A(\hat{\gamma})}{B(\hat{\gamma})} \right), \mathbf{I} \text{ is identity matrix} \quad (12)$$

and

$$\boldsymbol{\Gamma}(\hat{\gamma}) = \frac{1}{n} \sum_{i=1}^{n} \int_0^{\tau} \begin{pmatrix} \hat{a}_i + \hat{\alpha}_i \\ \hat{b}_i \end{pmatrix} \left(\hat{a}_i' + \hat{\alpha}_i', \quad \hat{b}_i' \right). \quad (13)$$

Let $A(\hat{\gamma}) = \lim_{n \to \infty} \sum_l A_l(\hat{\gamma})$ and $B(\hat{\gamma}) = \lim_{n \to \infty} \sum_l B_l(\hat{\gamma})$,

$$A_l(\gamma) = \frac{\partial \phi_l(\gamma)}{\partial \gamma} \quad (14)$$

and

$$B(\gamma)=\frac{\partial U(\gamma)}{\partial \gamma}. \quad (15)$$

Also, $\hat{a}_i$, $\hat{b}_i$ and $\hat{\alpha}_i$ are given in Equation (16)-(18).

$$\hat{a}_i=\int_0^{\tau}\left(Z_i-\bar{Z}\right)W(t)\,d\hat{\Lambda}_l(t) \quad (16)$$

$$\hat{b}_i=\int_0^{\tau}\left\{Z_i-\frac{S^{(1)}(t,\hat{\gamma})}{S^{(0)}(t,\hat{\gamma})}\right\}\left\{dN_i(t)-I(t\le T_i)\exp(\hat{\gamma}Z_i)\,d\hat{\Lambda}_0(t)\right\} \quad (17)$$

and

$$\hat{\alpha}_i=\int_0^{\tau}\left\{\frac{R(t)}{S^{(0)}(t,\hat{\gamma})}\right\}\left\{dN_i(t)-I(t\le T_i)\exp(\hat{\gamma}Z_i)\,d\hat{\Lambda}_0(t)\right\} \quad (18)$$

where

$$R(t)=n^{-1}\sum_{i=1}^{n}\left(Z_i-\bar{Z}\right)\int_0^{\tau}\frac{N_i(t)dN^*}{\exp(\hat{\gamma}Z_i)}. \quad (19)$$

3. SIMULATION STUDY

The Monte Carlo simulation study is conducted with k = 1 and condition on given treatment group covariate Z_i where $Z_i = 0$ for i in s_1 (group 1) and $Z_i = 1$ for i in s_2 (group 2). All of the results are based on 5000 replications at a significance level of $\alpha = 0.05$. The computation for the simulation was carried out in written R function using version 3.2.5 of the R statistical software.

The number of observation for subject i, m_i is generated based on $m_i = \exp(\gamma Z_i)$, $\gamma = 0$ means the observation processes between treatment groups are equal. For unequal observation processes, $\gamma = 0.1, 0.2, 0.3$. Given m_i, the follow-up times T_{i1}, $T_2, \ldots, T_{imi}$ for subject i are sampled from Uniform distribution over $(0,\tau)$ with $\tau = 10$ and $\tau = 20$ and the censoring time of subject i, C_i is the last follow-up time of subject i, $T_{imi.}$ Then, $t_1, t_2, \ldots, t_m$ is the unique order statistics of m observations of all follow-up times. The panel count data N_i's are generated based on

$$N_i(T_{i,j})=N_i(T_{i,1})+\left\{N_i(T_{i,2})-N_i(T_{i,1})\right\}+\cdots+\left\{N_i(T_{i,j})-N_i(T_{i,j-1})\right\}$$

and

$$N_i(T_{i,j}) - N_i(T_{i,j-1}) \sim Poisson\left(v_i \lambda_0(t_{i,j} - t_{i,j-1}) \exp(\beta Z_i)\right)$$

where $\lambda_0(t) = 1$, $\beta = 0.1, 0.2, 0.3$.

For mixed Poisson processes, v_i's are generated from Gamma distribution with shape parameter 2 and scale parameter of 0.5. For illustration, the data generated with $\gamma = 0.2$, $\beta = 0.2$ and $\tau = 10$ is showed in Fig. 3.

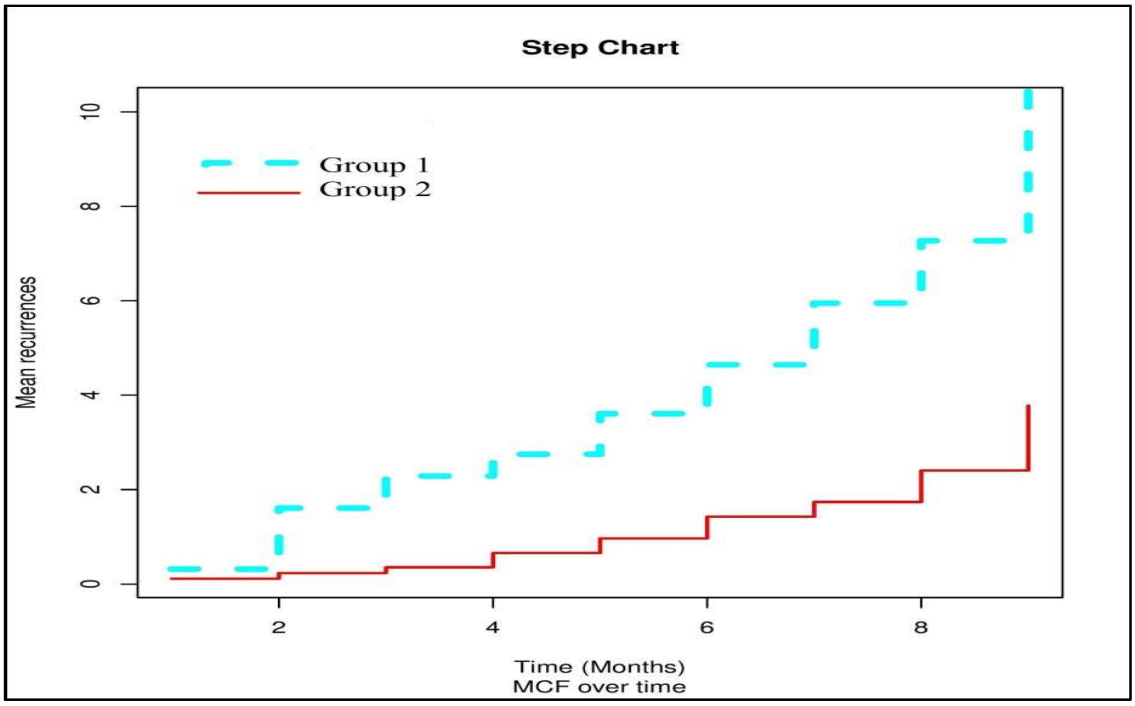

Fig.3. Step chart of the simulated data for cumulative mean recurrences

The test's performance is investigated through its power which is also the percentage of the test rejecting the false null hypothesis. The null hypothesis of testing no difference between mean cumulative function of treatments is rejected if p-value is less than 0.05. The asymptotic approximation of the test in Equation (10) is checked through the plot of the standardized test statistic against its theoretical quantile, which is showed in Fig. 4.

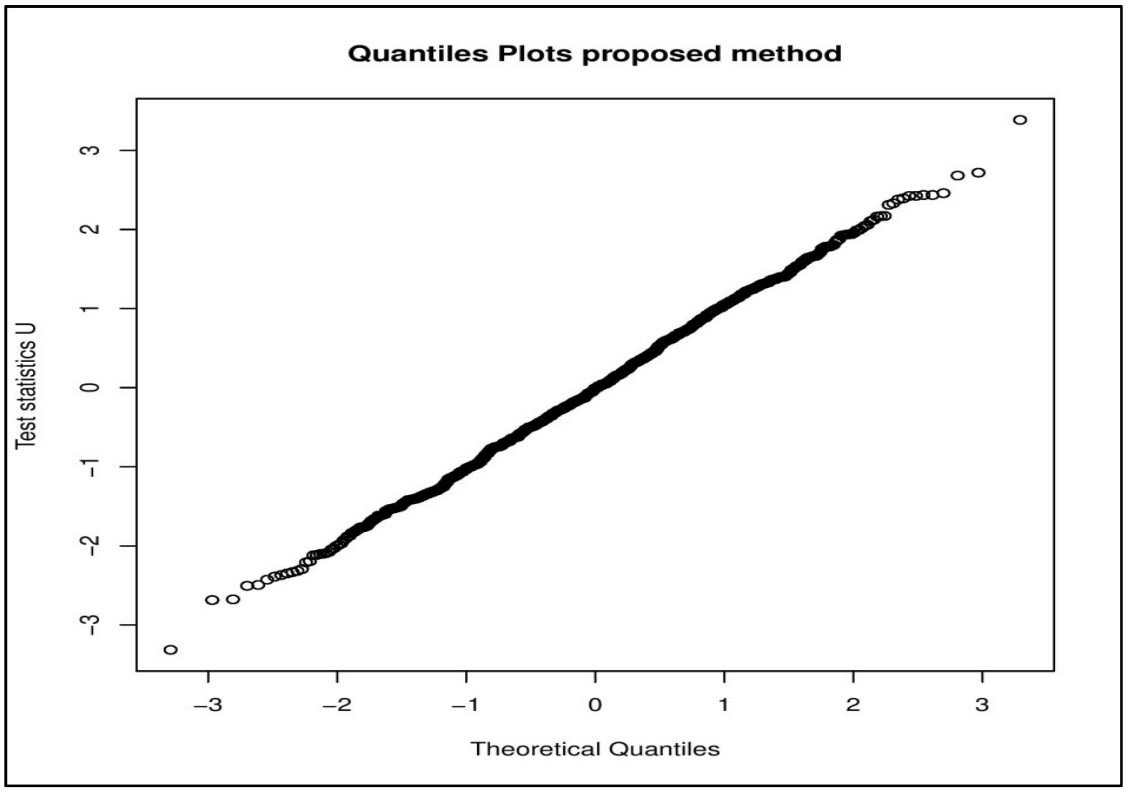

Fig.4. Quantiles plot of standardized test statistics with $n_1=n_2=50$ and $\gamma=\beta=0.2$

The asymptotic approximation of the test for $W_n^{(1)}$, n = 100 given in Fig. 4 is quite good. Similar plots are obtained for other tested situations. The asymptotic approximation of the test statistics get closer to normal distribution as the sample size increased.

Tables 1 present the power of the proposed test for $\tau = 10$ and $\tau = 20$ respectively. The power of the test procedures increase when the sample sizes increase. Similar results are obtained for when the length of follow-up period increased from $\tau = 10$ to $\tau = 20$. Overall, the performance of the proposed test gives a good power to detect treatment differences under the tested situations. In [12] showed that the test worked well even when the sample sizes were imbalanced between two treatment groups.

Table 1. The empirical power for the proposed test

			$\tau = 10$			$\tau = 20$		
γ	**n_1**	**n_2**	**β = 0.1**	**β = 0.2**	**β = 0.3**	**β = 0.1**	**β = 0.2**	**β = 0.3**
0	10	10	0.9584	0.9648	0.9662	0.8970	0.8606	0.9130
	15	15	0.9818	0.9830	0.9800	0.9862	0.9832	0.9758

	30	30	0.9866	0.9890	0.9818	0.9950	0.9940	0.9938
	50	50	0.9986	0.9994	0.9986	0.9996	0.9996	0.9998
0.1	10	10	0.9650	0.9710	0.9666	0.9596	0.9324	0.9624
	15	15	0.9858	0.9878	0.9848	0.9868	0.9848	0.9798
	30	30	0.9920	0.9880	0.9866	0.9980	0.9982	0.9952
	50	50	0.9996	0.9984	0.9990	0.9984	0.9992	0.9976
0.2	10	10	0.9608	0.9712	0.9560	0.9302	0.9306	0.9308
	15	15	0.9778	0.9716	0.9576	0.9942	0.9920	0.9864
	30	30	0.9932	0.9912	0.9798	0.9958	0.9952	0.9874
	50	50	0.9988	0.9988	0.9986	0.9986	0.9996	0.9986
0.3	10	10	0.9718	0.9604	0.9625	0.9482	0.9154	0.9136
	15	15	0.9810	0.9782	0.9716	0.9888	0.9830	0.9812
	30	30	0.9942	0.9922	0.9814	0.9944	0.9882	0.9888
	50	50	0.9992	0.9996	0.9994	0.9972	0.9978	0.9978

4. BLADDER TUMOUR STUDY

The nonparametric test described in previous sections will be illustrated by reproduced the data from the Veterans Administration Co-operative Urological Research Group (VACURG) and the data are presented in [1]. The original data consist of patients with history of superficial bladder tumours and treated with placebo, thiotepa and pyridoxine treatments. The third treatment pyridoxine was not included in the first part of data analysis as it did not have significant effect in reducing the recurrence of bladder tumour as discussed in [4, 10]. However, the results of multi-sample comparison are shown in Table 2 for comparison with existing nonparametric methods[3,16, 19].

The data consist of 85 patients with 47 patients assigned in placebo group and 38 patients in thiotepa group. The observed data included the follow-up time and the numbers of recurrent tumours during the follow-up study as well as additional information on baseline covariates on the size of the largest initial tumour and the number of initial tumours. The initial tumours were removed before enter to 53 months of follow-up. The multiple recurrences of tumours during the study are recorded.

Fig. 5 shows the mean cumulative functions of occurrence of the bladder tumours for both treatment groups. It appears to be not much difference in early follow-up, but over time, it's seem to be different and are proportional to each other. The patients treated with placebo treatment have higher recurrences compare to those treated with thiotepa treatment. Additionally, the thiotepa treatment seems to be effective in reducing the recurrences of bladder tumours where the occurrences of bladder tumours are not obvious. Thus, the main interest is to test whether the treatment difference is statistically significant.

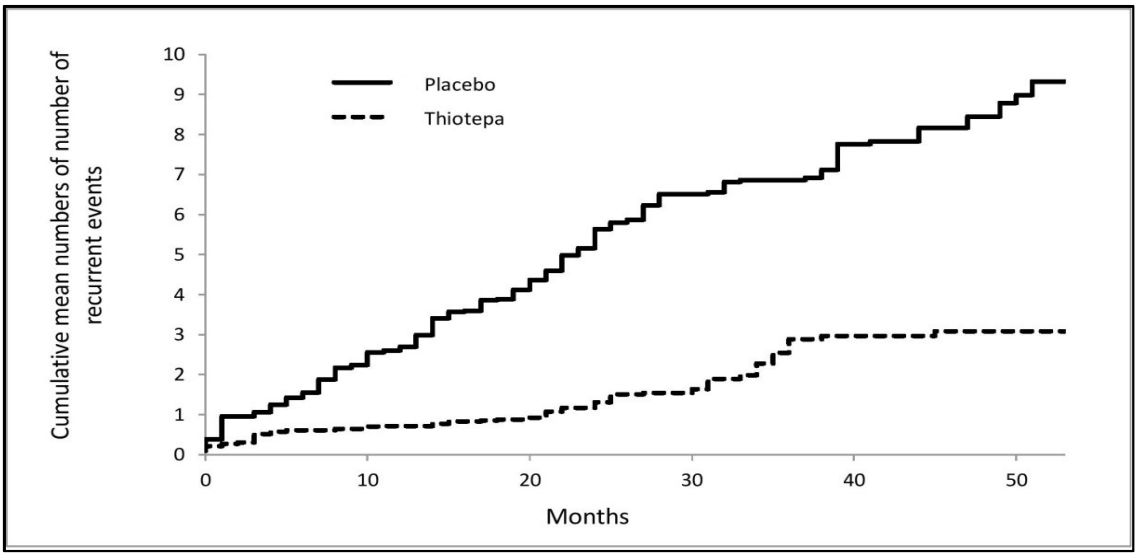

Fig.5. Mean cumulative number of recurrence tumours

Let Z = 0 for patients who treated with placebo and Z = 1 for patients who treated with thiotepa. The proposed test wascarried out under different weight processes describe in Equation (20) - (22).

$$W_n^{(1)}(t) = 1 \tag{20}$$

$$W_n^{(2)}(t) = n^{-1}\sum_{i=1}^{n} I\left(t \le t_{i,m_i}\right) \tag{21}$$

$$W_n^{(3)} = 1 - W_n^{(2)} \tag{22}$$

Based on the use of weight process $W_n^{(1)}$, $W_n^{(2)}$ and $W_n^{(3)}$, the proposed test yielded T*=3.5028, 3.3064 and 3.7795 with p-values of 0.0613, 0.069 and 0.0519 respectively. The proposed test rejects the null hypothesis at 10% level of significance.These indicated that the mean recurrence of the bladder tumours is significantly different across treatment groups.The

proposed test has similar conclusion as discussed in [4, 10], where the treatment differences are statistical significance.

Table 2 shows the comparison of the proposed method with existing nonparametric methods where in [3] based on nonparametric maximum likelihood estimator (NPMLE) and in [16] based on nonparametric maximum pseudolikelihood estimator (NPMPLE), both assumed identical observation processes while in [19] based on isotonic regression estimator (IRE) which assumed unequal observation processes across treatment groups.

Table 2.P-values comparison for Multi-sample test on bladder tumour data

Test		**W(1)**	**W(2)**	**W(3)**
Proposed Test	Test statistics	6.6215	6.0534	5.3456
	p-values	0.0365	0.0485	0.0691
[3]	Test statistics	3.617, 3.269	1196123, 300179	489000, 121908
	p-values	0.164, 0.195	$<10^{-8}$	$<10^{-8}$
[16]	Test statistics	4.9281	3.8682	4.9527
	p-values	0.0851	0.1445	0.0840
[19]	Test statistics	5.2805	0.0379	21.7701
	p-values	0.0713	0.9812	0.00002

The test results of [3] based on NPMLE are more significant than others methods with $W_n^{(2)}$ and $W_n^{(3)}$, while the unweighted test failed to detect the treatment difference. On the other hand, test based on [16, 19] failed to reject the null hypothesis with $W_n^{(2)}$.This may be due to the test based on the use of isotonic regression estimator of the mean functions crossing at the early to middle follow-up time. In [19] showed that the treatments are significantly different at late follow-up period at 5% level of significance. In [16] suggested that the treatment differences are significant at 10% level of confidence with weight process $W_n^{(1)}$ and $W_n^{(3)}$.

It appears that the proposed test is more effective than the existing tests in detecting the departure from null hypothesis with all three weight processes. The results also show that in [16] which assumed the observation processes are independent and identical across treatment groups is less significant as compared with the methods which considered unequal observation processes. In the presence of different observation processes, the tests assume the

observation processes are identical across treatment groups might provide misleading results. However, in [3] with weighted test gives significance results due to the estimator used are more efficient than other estimator as showed by [13]. Thus, one should choose the right test with proper weight process as most of the existing nonparametric comparison procedures are applicable to pre-schedule observations, where the observation processes across treatments are identical.

5. CONCLUSION

This paper discussed the distribution free test to compare treatment efficiency in medical follow-up study when the observation processes are differed across treatments. Based on the simulation study and the bladder tumour case study, the proposed test works well for situations consider here. Most of the existing nonparametric test for panel count data assumed identical observation processes between treatments [2-3, 8-9, 16, 20]. In reality, this assumption might not be true as shown in bladder tumour case study and might provide misleading results. Thus, one should carefully choose a test procedure based on the tested situations.

There exist limited study on nonparametric test and a lot of further works still need to be done. The proposed test is concerned on univariate nonparametric comparisons with time independent covariate. One might consider the case for time dependent covariates. Also, the proposed test is depending on the assumption of independent censoring. In order words, the censoring processes are independent of the observation processes and the recurrent processes. Furthermore, researcher might be interest in studying the treatment differences for bivariate or multivariate cases for future study or consider informative censoring cases as in [17-18].

6. ACKNOWLEDGEMENTS

The authors are grateful to the editor and referees for their careful reading of the paper. The research was supported by the Malaysia Ministry of Higher Education fund MyBrain15 and Putra grant (No. 9483600).

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How to cite this article:
Tan P L, Ibrahim N A, Adam M B, Arasan J. Multi-sample nonparametric treatments comparison in medical follow-up study with unequal observation processes through simulation and bladder tumour case study. J. Fundam. Appl. Sci., 2017, *9(6S), 147-161.*