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Distribution Free Test for Unequal Observation of Panel Count Data with Application in Medical Follow-Up Study

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Abstract

Objectives: In medical follow-up study, patients are treated with different treatments may have different follow-up schedule and the number of patients assigned in each treatment group may not be balanced. To address this, a nonparametric test procedure is proposed. **Methods/Statistical Analysis:** The proposed test statistics is constructed based on the integrated weighted differences between the mean cumulative function of the recurrences event with condition on treatment group. For performance evaluation, the empirical power of proposed test statistics are evaluated via Monte Carlo simulation study conducted using R statistical software. **Findings**: Based on simulation results, the proposed method gives a good power for both identical and unequal follow-up processes, even when the sample sizes are imbalanced. **Applications/Improvement:** The proposed test procedure is also applied to a set of panel count data arises from the National Cooperative Gallstone Study to compare the treatment efficiency. The proposed test procedure able to detect treatment differences and is in line with earlier research.

Keywords: Panel Count Data, Nonparametric Test, Treatment Comparisons, Unequal Observation Processes

1. Introduction

Panel count data arising from medical follow-up studies, where the study subjects could experience recurrences of the same event repeatedly and are observed only at discrete time points. In this case, only the numbers of recurrences between subsequent observation times are recorded. Due to lack of information, it is convenience to compare the treatment effects by means of the average rates or mean recurrences across treatments.

Example of panel count data is given in the National Cooperation Gallstone Study which consists of visit times in weeks and the observed counts of occurrences of nausea for 113 patients with floating gallstones treated with high-dose cheno (65) and placebo (48) groups over the first 52 weeks of follow-ups.[1,8,12-14] The actual visit times for the patients in gallstone study were differed even though they were scheduled for clinical observations at 1, 2, 3, 6, 9, and 12 months during the follow-up study. It is crucial to assess the effect of the treatments in reducing the symptoms of gallstone disease. Thus, it was hypothesized to determine whether there exists a significant difference between the average recurrences of nausea/vomiting symptoms for the patients in both treatment groups.

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Many authors have discussed the analysis of panel count data in the medical follow-up study included mean functions estimation, treatment comparisons and regression analysis.[1-22] Most of the existing nonparametric methods assumed that the observation processes are identical between treatment groups which may not hold in practice and may lead to misleading results.[1,3, 8,12,13,21,22] As panel count data involves repeated measurement of the recurrent event on the same subject at multiple discrete observation time points which may vary from patient to patient and the number of subjects may be relatively small and imbalanced between treatment groups. There exists a limited study on nonparametric methods which considered nonparametric comparison when observation processes are different across treatment groups and others considered regression methods.[4,5,18,20]

In this article, an alternative nonparametric comparison procedure is established based on the integrated weighted differences between the Mean Cumulative Function (MCF) of the underlying recurrent event with condition on treatment group when the observation processes which defining the total number of clinical visits and visit times are not identical across treatment groups. The performance of the proposed nonparametric test statistics is also examined for the situation when the sample sizes are imbalanced and relatively small between treatment groups.

In next section, a nonparametric test procedure will be proposed to allow unequal observation processes with relatively small and imbalanced sample sizes between groups. The performance of the proposed test procedure will be tested in various situations via Monte Carlo simulation study and the results are shown in Section 3. The simulation study was conducted using R statistical software. In Section 4, the proposed test procedure will be applied to gallstones study with discussions. Finally, some concluding remarks and future works will be given in Section 5.

2. Nonparametric Treatments Comparison

Consider $k + 1$ different treatment groups with total sample size of n independent subjects and each subject experiences recurrent events during the follow-up study. Let n_l denote the number of subjects in the lth group, $l = 1, \ldots, k + 1$, where $n_1 + n_2 + \ldots + n_k = n$. Also let $N_i(t)$ denote the counting process of the total number of recurrent event that have occurred up to time t from subject i with $\Lambda_i(t|Z_i) = E\{N_i(t)|Z_i\}$, the conditional expected number of recurrent events up to t per subject of $N_i(t)$ given Z_i. Where Z_i is a treatment indicator associated with subject i, $i = 1, \ldots, n$.

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 $T_{i,1} < T_{i,2} < \ldots < T_{i,j}$, $j = 1, 2, \ldots, m_i$ with m_i representing the total number of observation time points. Let C_i denote the censoring time of subject i and τ be the longest follow-up time.

In practice, the recurrences rate is usually non-constant, thus, the number of recurrences is assumed to follow a non-homogeneous Poisson process. To deal with the situation of unequal observation processes, let N_i followed a non-homogeneous Poisson process conditioning on covariate Z_i through the proportional model given in [1-2] with the intensity function

$$\lambda\left(t|Z_i\right) = \lambda_0\left(t\right)\exp\left(\gamma Z_i\right) \qquad (1)$$

where $\lambda_0(t)$ is known baseline mean and γ is unknown regression parameters. Model above also implies that Z_i has a multiplicative effect on the number of observations, where the difference across treatment groups is given by $\exp(\gamma Z_i)$ and when γ=0 means the observation processes are identical.

Under model (1) and conditional on Z_i,

$$E\left\{\sum_{j=1}^{m_i} N_i \left| Z_i \right.\right\} = \int_0^\tau \mu(t) S_i(t) \exp(\bar{\gamma} Z_i) \lambda_0(t)\, dt \tag{2}$$

where $S_i(t) = P(t \le C_i)$ and $\mu(t)$ denote the common mean function of $N_i(t)$ under hypothesis H_0. Thus

$$\exp(\hat{\gamma} Z_i)^{-1} E\left\{\int_0^\tau N_i(t)\, dN_i^*(t)\right\} = \int_0^\tau \mu(t) S(t) \lambda_0(t)\, dt \tag{3}$$

where

$N^*(t) = 1/n \sum_{1=1}^{n} \sum_{j=1}^{m_i} I(T_i \le t)$ is proportion of observation.

Then, the test statistics could be formulated based on (3). The total count of recurrences with condition on treatment group l up to time t is written as

$$\tilde{N}_l(t) = \int_0^t \frac{N_i(s)\, dN_i^*(s)}{\exp(\hat{\gamma} Z_i)} \tag{4}$$

and the MCF for treatment group l up to time t is computed as

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

$Y_i(t) = I(t \le C_i)$ denote the at risk indicator prior to time t.

Motivated by the Wilcoxon-type of statistics, the proposed test statistic is given below

$$\phi_l(\hat{\gamma}) = \frac{1}{\sqrt{n}} \sum_{i \in s_l} (Z_i - \bar{Z}) \int_0^\tau W_l(t)\, d\left\{\hat{\Lambda}_l(t) - \Lambda_0(t)\right\} \tag{6}$$

γ can be estimated by solving the partial likelihood score given in (7).[1-2]

$$U(\gamma) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \int_0^\tau \left\{ Z_i - \frac{S^{(1)}(t;\gamma)}{S^{(2)}(t;\gamma)} \right\} dN_i^*(t) \tag{7}$$

Where

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

and

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

When hypothesis null H_0 is true, by Taylors series expansion[19-20], $\phi(\hat{\gamma}) = \phi(\gamma) + A(\gamma) B^{-1}(\gamma) U(\gamma)$ are independent and asymptotically normal with mean zero and covariance matrix

$$\mathbf{V}(\hat{\gamma}) = \mathbf{H}(\hat{\gamma}) \mathbf{\Gamma}(\hat{\gamma}) \mathbf{H}(\hat{\gamma})' \tag{10}$$

where,

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

Let

$$(\hat{}) \quad \frac{\partial \phi(\hat{\gamma})}{\partial \hat{}}$$

$$B(\hat{\gamma}) = \frac{\partial U(\hat{\gamma})}{\partial \hat{\gamma}}$$

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

where

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

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

and

$$\hat{\alpha}_i = \int_0^{\tau}\left\{\frac{n^{-1}\sum_{i=1}^{n}\tilde{N}_i(t)}{S^{(0)}(t,\hat{\gamma})}\right\}\left\{dN_i^*(t) - I(t \le T_i)\exp(\gamma Z_i)\,d\hat{\Lambda}_0(t)\right\}.$$

Then, the null hypothesis test can be performed based on the statistic $U = \phi(\hat{\gamma})\mathbf{V}^{-1}(\hat{\gamma})\phi(\gamma)'$, where the null distribution can be approximated by a chi-square distribution with k degree of freedom.

3. Simulation Study

The simulation study is focused on two-sample comparison problem, where k=1 and conditional on given treatment group covariate Z_i, where Z_i=0 for control group and Z_i=1 for treatment group. The number of observation times m_i was sampled from Poisson distribution with mean $\exp(\gamma Z_i)$, where γ=0, which also indicates that the observation processes for both treatment groups are identical, otherwise γ=0.2. Given m_i, a panel observation times T_i were taken to be the order statistics of m_i observations sampled from Uniform distribution over (0, τ). The censoring time C_i is the largest observation time of subject i, and the follow-up period of all subjects is set as τ=10 and τ=20. The panel count data were generated from Poisson distribution with the mean given in (1) based on

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

All of the results were based on 1000 replications at a significance level of α = 0.05. The null hypothesis of testing the equality of mean recurrences between treatments is rejected if p-value < 0.05. The performance of the proposed test is assessed through its power. The power is measured by the mean frequency of the test statistic in rejecting the falsely stated null hypothesis. The asymptotic behavior of the proposed test in (6) is assessed through the quantiles plot of the standardized test statistic against normal distribution.

All test statistics were constructed using the weight process $W_n(t)$ that is commonly used in the analysis of recurrence events.[3] For simulation study, $W^{(1)}$ is used to put an average weight over the period of follow-up. Second choice of weight process $W^{(2)}$ is weighted at early to middle period of follow-up, which are the weights proportional to the number of the subjects still under follow-up. The third choice $W^{(3)}$, on the other hand, weighted at late period of follow-up. The weight processes are listed as follow.

$$W_n^{(1)}(t) = 1$$

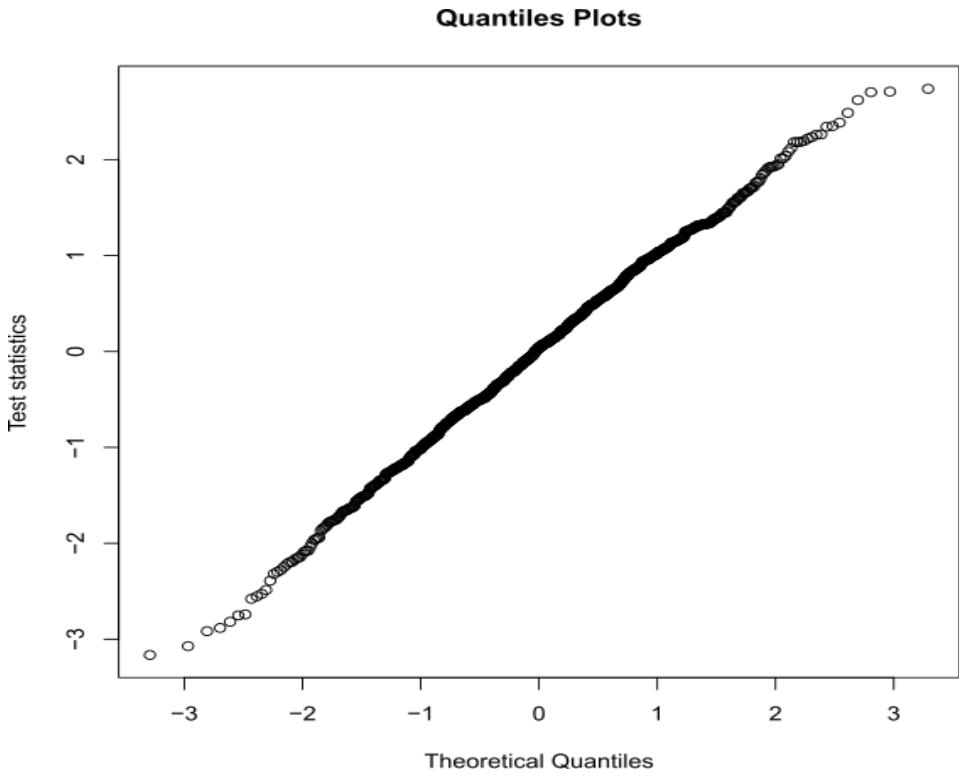

Figure 1. Q-Q plot of the proposed test for n0=30, n1=50, γ=0.2, τ=10 and $W^{(1)}(t)$.

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

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

4. Results and Discussion

Quantiles plot for the proposed test against the standard normal distribution is plot to investigate whether the asymptotic distribution of the proposed test derived here is satisfactory. Figure 1 indicated that the normal approximation of the proposed test is reasonably well in this setting. Similar plots were obtained for other situations based on simulation data.

Table 1 gives statistical power of the proposed test procedure based on 1000 replications of Monte Carlo simulation. Overall, the proposed test procedure gave a good power to detect the departure from null hypothesis under all tested situations. The effect of the length of follow-up periods on the test performance is not obvious. The power of the test procedures increased when the sample size increased and the more balanced of the sample sizes between the two groups, the better the power. Similar results were obtained by using other values of γ, which the simulation results were not included here.

Table 1. Monte Carlo simulation results of mean frequency of rejection at 5% level of significance

			W^1		W^2		W^3	
γ	n_0	n_1	τ=10	τ=20	τ=10	τ=20	τ=10	τ=20
0	10	20	0.7750	0.8230	0.8090	0.8500	0.7150	0.7660
	10	30	0.9430	0.9260	0.9550	0.9240	0.9230	0.8770
	10	50	0.9770	0.9810	0.9750	0.9780	0.9690	0.9820
	30	50	0.9890	0.9770	0.9850	0.9500	0.9850	0.9810
	50	50	1.0000	1.0000	1.0000	0.9930	1.0000	1.0000
0.2	10	20	0.7860	0.9050	0.8050	0.9150	0.7350	0.8440
	10	30	0.9090	0.9340	0.9120	0.9210	0.8760	0.8880
	10	50	0.9540	0.9680	0.9550	0.9560	0.9620	0.9690
	30	50	0.9570	0.9520	0.9350	0.9320	0.9630	0.9640
	50	50	1.0000	1.0000	0.9950	0.9960	0.9990	0.9960

5. Application

The proposed test procedure is applied to a set of panel count data arising from gallstone study discussed early in Section 1. Figure 2 portrayed the observation processes between treatments. In general, it is clearly showed that the patients in high-dose cheno group visit clinic more often than patients in placebo group. Thus, the existing methods that assumed identical observation processes between treatments might produce misleading results.

The main interest is to compare the treatment effects in reducing the incidences of nausea. Placebo group is treated as control group (Z_i=0) and the high-dose cheno group as treatment group (Z_i=1). Figure 3 portrayed the mean cumulative count of the number of episodes of nausea for placebo and high-dose cheno treatments for the first 52 weeks of follow-ups.

There is a clear difference in mean recurrences of nausea during the early to middle period of follow-up between high-dose cheno and placebo groups. The MCF between two groups crossed each other at the late period of follow-up. The patients in the placebo treatment group seem to experience incidences of nausea more than the patients treated with high-dose cheno treatment over the first 50 weeks. It showed that high-dose cheno treatment is effective in reducing the incidences of nausea in early treatment. However, the incidences of nausea experienced by patients in the high-dose group seem to change steadily after week 50. This may be due to some patients

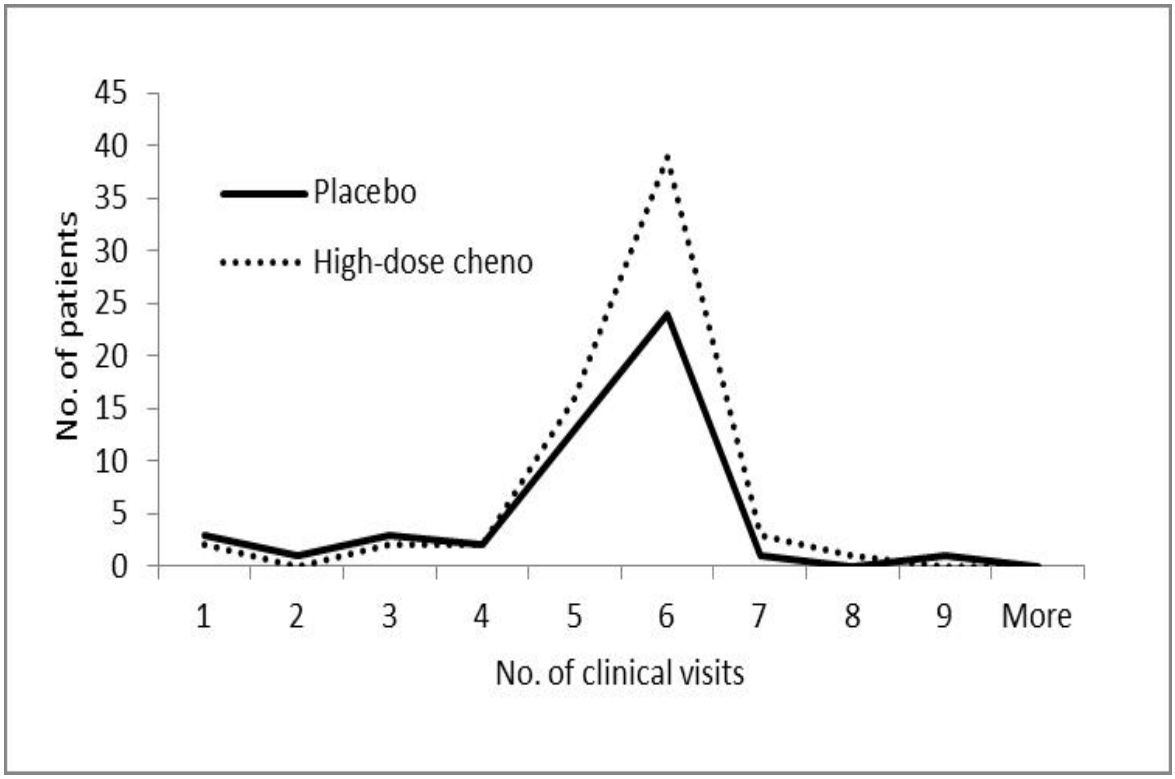

Figure 2. Distribution of clinical visits for patients in placebo and high-dose cheno treatment groups.

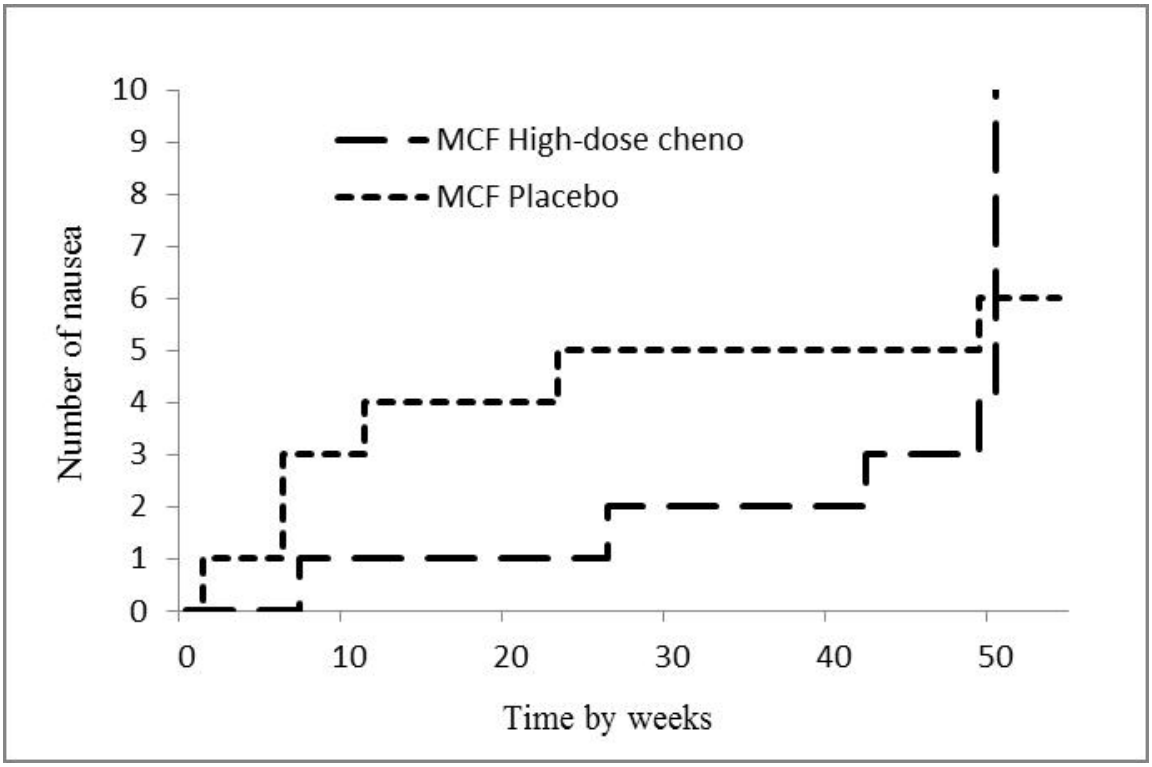

Figure 3. Mean cumulative counts of incidences of nausea.

who have experienced relatively high numbers of nausea than others (patients 13, 25, 50, 57, 78, 89 and 109). Specifically, patient 25 have 99 recurrences in week 52 and patient 50 have 40 recurrences in week 51.

The proposed method is applied to test on the hypothesis of no treatment difference and the results are listed in Table 2. The proposed test procedure failed to reject the null hypothesis at 0.05 level of significant. However,

Table 2. Test results for gallstone data

Weight process	$W^{(1)}$	$W^{(2)}$	$W^{(3)}$
Statistic	3.2908	3.6558	2.1841
***p*-value**	0.0697	0.0559	0.1394

Table 3. Test results for gallstone data with reduced data

Weight process	$W^{(1)}$	$W^{(2)}$	$W^{(3)}$
Statistic	3.8036	3.9754	2.5480
***p*-value**	0.0511	0.0462	0.1104

the treatment effect was significant at 0.10 with weight processes $W^{(1)}$ and $W^{(2)}$. The weight process $W^{(2)}$ is more preferable than $W^{(1)}$ in detecting the treatment differences in this case, where the result of weight process $W^{(1)}$ is less significant than weight process $W^{(2)}$. The weight process $W^{(3)}$ showed no significant treatment difference between two groups, this may be due to the crossing of the mean cumulative functions at the late follow-up times which may contribute to a lower power to detect the difference.

The patients with relatively high number of recurrences of nausea were then removed from complete data list and the hypothesis testing was rerun to investigate their effects on the proposed test results. The results based on reduced data are listed in Table 3 and suggested that the mean recurrences of nausea is significantly different between two treatments with weight process $W^{(2)}$ at α=0.05 and with weight process $W^{(1)}$ at α=0.10. Similarly, the test result with weight process $W^{(3)}$ showed no significant treatment difference between two groups.

The test procedures which assumed the observation processes were identical distributed between treatments failed to detect the difference between two treatments.[1,8,12,13] However, the test procedure based on Nonparametric Maximum Likelihood Estimator (NPMLE) with weight processes $W^{(2)}$ and $W^{(3)}$ suggested that the treatment difference between the two treatments was significant.[12] This may be due to NPMLE is more effective than the isotonic regression estimator and nonparametric pseudolikelihood estimator as shown by Wellner and Zhang.[6] Furthermore, the selection of the weight processes becomes crucial in comparing the treatment effect. The proposed test with appropriate weights suggested that the incidences of nausea were significantly different across treatment groups, and in line with the results given in earlier research.[12,14]

6. Conclusion

Previous developments in the field of nonparametric tests for panel count data were focused on the use of mean function estimators and assumed that all subjects under study have same observation time.[1,3,8,2,13,21,22] In practice, this assumption may be violated as seen in the example discussed in Section 4. There exist limited works related to unequal follow-up problem.[4,5,18-20] This paper proposed a nonparametric test for comparing the conditional mean cumulative functions across treatment groups based on Wilcoxon type of statistics. The performance of the presented method is tested for more general situations where there exist unbalanced samples with relatively small sample sizes. The pooled sample sizes should be at least 30 for

well normal approximation. The proposed test works well for practical situations based on simulation studies and real data analysis.

The proposed approach can be applied to more general situations as compare to existing methods.[1,3,8,12,13,21,22] However, the proposed test relies on the assumption that the observation process and the recurrent event process were independent given treatments. This might not always be the case in real data analysis; the occurrences of the events of interest may be correlated with censoring time or other covariates. Thus, one should consider the case with informative censoring and developed for nonparametric treatment comparison. Furthermore, the case considered here is univariate with time-independent covariate; the proposed test could be extended to multivariate case or time-dependent covariate. One might want to replace the conditional mean cumulative functions with nonparametric maximum likelihood estimator for future research as it may be more efficient but needs a great deal of computational effort and its asymptotic properties is unknown as there is very limited research available.

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