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Statistics

MODELLING RECURRENT EVENTS OF HOSPITALIZATIONS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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ABSTRACT Hospitalizations often occur multiple times during the disease course of a Systemic Lupus Erythematosus (SLE) patient. However, modelling of recurrent hospitalizations has not been fully explored. We investigated the association between patient factors and the risk of hospitalization among patients with SLE using an extension of the Cox model for the analysis of recurrent events such as Andersen and Gill [AG] model, Prentice, Williams and Peterson Total Time [PWP-TT] & Gap Time [PWP-GT] model. Over the follow-up of 1.5 years for 75 patients, more than 157 hospitalizations for which recurrence ranged from one to six were observed. The median follow-up time for the first hospitalization event was 113 days and it increases for the consecutive recurrent events. The common reasons for recurrent hospitalization in SLE patients are Flare (85.1%), Infection (10.3%) and Movement Disorder (4.6%). The importance of patient factors for the risk of being admitted to hospital was variable over the course of the disease. Conditions such as flare, infection and movement disorder had a sustained association with the rate of hospitalization across all episodes examined. The analysis of recurrent events can explore the longitudinal aspect of SLE and the critical issue of hospitalizations in this population. We recommend that the PWP models are better suited than the AG model for the analysis of risk factors for hospital admission among SLE patients. Overall, the most trusted model for this data is stratified gap-time model for this dataset.

KEYWORDS : Recurrent Events, Multiple failure data, Survival Analysis, Systemic Lupus Erythematosus (SLE)

INTRODUCTION

Chronic autoimmune diseases often have repeated hospitalization in the disease course and associated clinical event histories for the patient population vary widely. We often see repeated occurrence of hospitalization in the same patient, such events refers as recurrent events. Unlike recurrent events, multiple failure events involve those repeated occurrences of the hospitalization that are not of same type but somewhat related such as hospitalization due to other comorbidities like myocardial infraction, diabetes, infection, etc. In survival analysis, such recurrent or multiple failure events are assumed to be correlated in same patient and adjustment for within-subject correlation should be done. If correlations between multiple failure events are ignored the null hypothesis is rejected and the confidence intervals (CI) for the estimated rates could be artificially narrow down.

Logistic regression or cox-proportional hazard modelling is the most common analysis techniques to evaluate risk factors but it will not be appropriate for multiple failure events at it consider only the first event and disregard the information of repeated events after the first event. There are many statistical literatures published over the last few decades about powerful survival analysis techniques for multiple failure event data to examine risk factors but are not commonly implemented.

Motivating Example: Recurrent Hospitalization in SLE Patients

Systemic Lupus Erythematosus (SLE) is such a chronic autoimmune illness with a remitting and relapsing course and variable presentation. It can affect multiple organ systems and holds the potential of having severe consequences in several organ systems [1]. With increased understanding of the disease process, survival of patients with SLE has improved over recent decades [2, 3]; however, disease morbidity still remains a significant issue [4] and hence clinical interest lies in repeated hospitalization of each patient and the dynamics of the disease progression over the follow up period. Several publications studied causes and predictors of hospitalization in patients with SLE [5]. These studies have shown similar causes of hospitalization, but the frequency of hospitalization for the different admissions has varied significantly, with hospitalizations for SLE flare ranging from 11% to 80.8% [5-8] and infectious causes of hospitalization ranging from 10.9% to 37% [4-8].

We studied SLE patients admitted in the Rheumatology Ward for hospitalization in V.S. Hospital, Ahmedabad, Gujarat over 1.5 years in order to study the different causes of repeated hospitalization and its relative risk among SLE patients. It helps to determine the changing reasons for hospitalization and economic burden of SLE. The hospital discharge sheet of patients has been interrogated to identify the SLE episodes and subsequent hospitalization for causes directly related to their disease, from October 2017 until April 2019. In addition following information was also collected: age, sex, caste, number of admissions per patient, reasons for hospital admissions and length of hospital stay, readmission, on medical records over time has been retrieved.

We review different variance corrected models for recurrent event data (the Andersen and Gill [AG] model, Prentice, Williams and Peterson Total Time [PWP-TT] & Gap Time [PWP-GT] model) and compare their results in an analysis and disease condition as a risk factor for different causes of hospital admission.

STATISTICAL MODELS FOR RECURRENT EVENTS

Anderson Gill Model (AG Model)

Andersen Gill model is a generalization of Cox proportional hazard regression model which assumes that the correlation between event times for a subject can be explained by the past events. AG model is suitable model when correlations among events for each individual are induced by measured covariates but the number of recurrence is not taken into account. The outcome of interest is in the overall effect on the intensity of the occurrence of a recurrent event. It uses a common baseline hazard function for all events and estimates a global parameter for the factors of interest. Every subject risk intervals contribute to the risk set for every event, irrespective of the number of events for each individual.

AG Model have counting process kind of data inputs where each subject represented as series of recurrent observation with given time as $(t_0,t_1]$, $(t_1,t_2]$ … $(t_m$, last follow-up time] where, each recurrent event for the i^{th} subject is assumed to follow a proportional hazard model is given as:

$$\lambda_i(t) = \lambda_0(t)exp\{\beta_k x_i(t)\}$$

Prentice, Williams and Peterson Models (PWP Models)

PWP models are of two types: PWP-TT (total time) model and PWP-GT (Gap time) model. PWP-TT model is for analyzing ordered multiple events considering each sequential event separately so that baseline hazard function can differ between the sequential events. Thus it is essentially a stratified proportional hazards model with time scale as the time from study entry. The PWP –TT model allows any covariate to have different associations with different sequential events. PWP-TT model considers that individuals are not at risk for the next event until the preceding event has occurred and terminated.

The hazard function for the k^{th} event for the i^{th} subject with the proportional hazard form is written as

$$\lambda_{ik}(t) = \lambda_0(t)exp\{\beta_k x_i(t)\}$$

PWP-GT model is also conditional model like PWP-TT as an individual is not considered in the risk set for the kth event until experiencing the $(k-1)^{th}$ event.

$$\lambda_{ik}(t) = \lambda_0(t - t_{k-1})exp\{\beta_k x_i(t)\}$$

$\lambda_{0k}(t)$ represents the event-specific baseline hazard for the kth event over time. The PWP - GT model describes an intensity process from the occurrence of an immediately preceding event, with the gap time defined as $(t- t_{k-1})$. PWP-GT model evaluates the effect of a covariate for the k^{th} event since the time from the previous event. When using a gap or waiting-time scale, the time index is reset to zero after each recurrence of the event, with assumption of a renewal process. Gaps between events are often useful with infrequent events, when a renewal occurs after an event or when the interest lies on prediction of a next event.

RESULTS AND DISCUSSION

There were a total of 75 SLE patients hospitalized during October 2017 to April 2019 resulting in 157 recurrent hospitalizations. Average age at hospitalization was 33.2 years (S.D. 11.6); 74(98.7%) of hospitalized patients were female. The demographic data and baseline characteristics are presented in Table1.

Table-1: Demographic and Baseline Characteristics

Variables	Statistics	N=75
Age (Years)	Mean(SD)	32.2(11.62)
Sex		
Female	n(%)	74(98.7)
Male	n(%)	01(1.3)
Caste		
Hindu	n(%)	45(60.0)
Muslim	n(%)	30(40.0)

Over the follow-up of 1.5 years, 75 SLE patients experienced hospitalization ranged from one to six. Table 2 shows a summary of follow-up times and number of patients with hospitalization for the consecutive recurrent events. The median follow-up time for the first hospitalization event was 113 days and it increases for the consecutive recurrent events.

The common reasons for recurrent hospitalization in SLE patients are broadly categorized listed in Table 3 as SLE Flare (85.1%), Infection (10.3%) and Movement Disorder (4.6%). The most common reasons for hospitalization related to Flare include Lupus Nephritis, NPSLE, Myositis, Musculoskeletal, Haematological and Lupus Flare, etc. The most common is Colitis for hospitalization due to infection and Chorea due to movement disorder.

Table 2: Summary of time between consecutive hospitalizations in SLE Patients

Recurrence	Follow-up Time (In days)			No. of Patient with SLE		
	Min	Max	Median	Event	Censored	Total
1	34	607	113	29	46	75
2	84	627	215	19	10	29
3	104	673	222	14	4	18
4	111	365	237	11	3	14
5	129	485	285	10	1	11
6	143	639	293	3	7	10

Table 3: Causes of Recurrent Hospitalizations

Reason for Hospitalizations (N=157)	n(%)
Flare	**149(85.1)**
Lupus Nephritis	55(36.9)
Neuropsychiatric Systemic Lupus Erythematosus (NPSLE)	19(12.8)
Myositis	15(10.1)
Musculoskeletal	12(8.1)
Haematological	7(4.7)
Lupus Flare	6(4.0)
Antiphospholipid antibody syndrome (AP LA)	4(2.7)
Vasculitis	4(2.7)
Agglutinin-Induced Hemolytic Anemia (AIHA)	4(2.7)
Neuropathy	3(2.0)
Renal	3(2.0)
Mucocutaneous	3(2.0)
Serositis	2(1.3)
Multiple Sclerosis	1(0.7)
Cutaneous	1(0.7)
Diffuse Alveolar Haemorrhage (DAH)	1(0.7)
Subarachnoid Haemorrhage (SAH)	1(0.7)
Pulmonary Artery Hypertension(PAH)	1(0.7)
Granulomatous	1(0.7)
Cytopenia	1(0.7)
IDA Hypothermia	1(0.7)
Scleroderma	1(0.7)
Intestinal Obstruction	1(0.7)
Target Lesions	1(0.7)
Refractory	1(0.7)
Infection	**18(10.3)**
Colitis	14(18.7)
Paripheral Gangerine	2(2.7)
Mayocard	1(1.3)
Atypical Pneomonia	1(1.3)
Movement Disorder	**8(4.6)**
Chorea	8(100)

We fit three models to identify the risk factors for recurrent SLE hospitalizations (Anderson Gill Model, PWP total time model and PWP gap time). Table 4 shows the parameter estimates from the three models for risk factors including Age, Caste, Flare, Infection and movement disorder. Here our interest lies in the association between each of the risk factors or predictors $(x_1, x_2,\ldots x_n)$ and the outcome i.e recurrent hospitalization. The associations are quantified by the regression coefficients $(\beta_1, \beta_2..\beta_k)$. The estimated coefficients represent the change in the expected log of the hazard ratio relative to a one unit change in X_1, holding all other predictors constant. The results from all the three models were qualitatively different except for age. The hazard ratio for age is close to 1 in all models and hence it does not affect the recurrent hospitalization holding all other predictors constant. The predictor caste Hindu as compared to Muslim has hazard ratio less than 1 in AG model hence it is protective i.e associated with improved disease course but as per PWP-TT and PWP-GT, the hazard ratio is greater than 1 i.e the expected hazard of recurrent hospitalization is higher in Hindus as compared to Muslims when all other predictors are constant. All the three models reveal that the risk factor of flare as compared to infection is more in SLE patients for recurrent hospitalization as the hazard ratio is greater than 1, holding all other predictors as constant. Also the risk of flare compare to movement disorder for recurrent hospitalization is very high as per AG model and PWP-GT model. This may not reveal in PWP-TT model as it consider each event separately so that baseline hazard function can differ between the sequential events.

CONCLUSION

In chronic autoimmune diseases like SLE, recurrent hospitalization is common in the course of disease with wide associated clinical event histories for the patient population. The analysis of recurrent events can explore the longitudinal aspect of SLE and the critical issue of hospitalizations in this population. Hence, it is very important to consider the use of as much data as possible and to conduct analysis that can enhance a comprehensive understanding of the role of the risk factors in the disease process. A variance corrected models

Table 4: Risk factors for SLE hospitalization recurrent event data using Variance-Corrected models

Variable	Model 1 (AG Model)		Model 2 (PWTT Model)		Model 3 (PWGT Model)	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	0.97 (0.93-1.01)	0.1564	0.98 (0.96-0.99)	0.0107*	0.97 (0.95-1.00)	0.0253*
Caste_Muslim	0.96 (0.43-2.14)	0.9206	1.23 (0.79-1.94)	0.3612	1.15 (0.72-1.84)	0.5619
Cause_Infection	1.06 (0.34-3.31)	0.925	1.10 (0.51-2.38)	0.8057	1.47 (0.71-3.05)	0.2997
Cause_Movement Disorder	2.28 (0.94-5.49)	0.0669	0.57 (0.33-0.96)	0.036*	1.67 (0.98-2.83)	0.0579
Abbreviation: HR=Hazard Ratio, CI=Confidence Interval, * p-value<0.05; Statistically Significant						

Andersen and Gill (AG) model, Prentice, Williams and Peterson Total Time (PWP-TT) model, and Prentice, Williams and Peterson Gap Time (PWP-GT) model) must be used for recurrent events. The advantage of these techniques compared to time to first event Cox modeling is that an individual is at risk throughout follow up period which is more suitable for recurrent type of events. Both AG model and PWP models estimate hazard ratios for the association of risk factors and failure events with the assumption of proportional hazard i.e the difference in the risk of failure events to a risk factors are time independent. However the underlying risk of failure is regarded as the same for each event within an individual in AG model whereas the PWP models allows this underlying risk to vary.

The importance of patient factors for the risk of being admitted to hospital was variable over the course of disease. Conditions such as flare, infection and movement disorder had a sustained association with the rate of hospitalization across all episodes examined. In the context of hospital admission among SLE patients, it is reasonable to expect that risk of hospitalization will increase with the accumulated number of previous admission and length of stay in the hospital. Therefore, we recommend that the PWP models are better suited than the AG model for the analysis of risk factors for hospital admission among SLE patients. Overall, the most trusted model for this data is stratified gap-time model for this dataset. The general conclusion would be that there seems to be marginal evidence that the treatment is effective at preventing the first recurrence of SLE episode, but no evidence that the treatment is effect at preventing future recurrences.

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