Research Article

Application of Parametric and Nonparametric Copula Marginal Models in Recurrent Failure Times of Childhood Seizures: Bayesian Approach

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Abstract

Seizures are the most common pediatrics neurologic disorder in children who are suffering at least one seizure in the first 16 years of life. Anyone at any age can have a seizure in certain circumstances, such as in meningitis, alcohol withdrawal, and other acute situations that anyone can experience. Survival analysis typically focuses on time to event data and recurrent events is a multivariate survival analysis in which event occurs more than once per subject over follow-up time. The study of recurrent events data is of particular importance in medical statistics. The most crucial issue in recurrent data is a correlation between relapses of each subject. This study aimed to identify some risks factors of the recurrent times of childhood seizures by fitting copula models using a Bayesian approach. In a retrospective study, Data of 300 seizure children who had at least one relapse within the study period has been analyzed. In this study, we modelled the joint distribution of recurrent events using parametric copulas within a Bayesian framework.

Results indicated a positive correlation between successive gap-times. The age at the beginning of the reception, sex, history of hospitalization, taken drugs, family history, evolutionary status and fever during the seizure were significant on the hazard of recurrent times to relapses. Results imply that according to the DIC criterion, the Basic Weibull-Clayton model was selected as the more suitable model. Existing correlation between relapse times requires continued efforts. To decrease relapse probability especially in children who experience relapses when have not taken drugs, children without history of hospitalization, children with fever during their seizure, who have family history of seizure, who have delay evolutionary status, the age at the beginning of reception of children higher than ten years and girl's special preventive and treatment efforts is recommended.

Keywords: Seizure; Meningitis; Bayesian Approach; Recurrent Events; Copula

Introduction

A Seizure is a transient, involuntary alteration of consciousness, behaviour or autonomic function caused by an excessive rate and hypersynchrony of discharges from a group of cerebral neurons. It is resulting from abnormal excessive or synchronous neuronal activity in the brain. During a seizure, cerebral blood flow, oxygen and glucose consumption, carbon dioxide and lactic acid production all increase. Brief seizures rarely produce lasting effects on the brain. Termination of the seizure is the first priorities in patients who are actively seizing [1]. Acute symptomatic seizures are secondary to an acute problem affecting brain excitability such as electrolyte imbalance or infection. Epilepsy is defined as recurrent, unprovoked seizures. Epileptic seizures are generally classified as focal (or partial), arising from one region of the cortex, or generalised seizures, which occur from both hemispheres, simultaneously [2]. Several cross-sectional studies have demonstrated that psychotic disorder and other psychiatric conditions for which antipsychotics may be prescribed are more common among people with epilepsy than in the general population [3]. Information about the seizure risks associated with newer antipsychotics is scarce [4]. Seizure relapses commonly occur in patients following long-term seizure remission. Treatment history and duration of epilepsy are predictive risk factors for both seizure relapses and the development of drug resistance [5].

Cumulative incidence studies under 15-year-old children indicate that 1.0-1.7% of children have had at least one seizure and 0.7-0.8% have had recurrent seizures [6-9]. Many studies have examined the risk of recurrence of seizures. The wide variation found in the risk of recurrence among those who have had first seizure seems to be explained by differences in study design or differences in the characteristics of the study groups. Overall, about 35 percent of patients with first seizure can be expected to have a second within the subsequent three to five years, although the

risk varies from less than 20 percent to 100 percent, depending on clinical characteristics [10-12].

Recurrent events are the natural outcomes in many biomedical and epidemiology studies. Modelling and analysis of gap-times, times between successive frequent events, is attractive in specific settings. Renewal processes focus on analyse the gap-times between consecutive events [13]. Analysis of successive gap-times conditional on event history is extensions of the renewal model to deal with dependent gap-times [14,15]. Few studies have assessed time to recurrent events, remission and recovery of patients using Cox regression model, but most of them failed to account the repeated feature of relapses and correlation caused by frequent events within- subjects [16-18]. Some individuals are more prone to experience their next disease relapses more quickly than other individuals. It implies heterogeneity across individuals and produces within-subject correlation in the times of recurrent events of the subject [19,20]. Frailty and copula models incorporate heterogeneity into the model affecting the parameters estimates [21].

The Copula-based approach allows to decouple the marginal distributions from the dependent structure and thus provides a direct interpretation of covariate effects on marginal distributions as well as on the multivariate association [22]. Estimation of copulas can be achieved fully parametrically by assuming parametric models for both the copula and the marginal, whereas nonparametric estimation specifies a parametric copula while leaving the marginal nonparametric [23]. An attractive Bayesian alternative is to construct inference from the joint posterior in a Monte Carlo function [24]. In this study, we have used the Clayton copula model with both parametric and nonparametric marginal baseline hazards using the Bayesian approach which accounts for time-dependent covariates and heterogeneity in repeated relapses of seizure disorder.

Methods

In a retrospective study, data in documents of 300 seizure children who had referred to Rofeideh and NoorAfshar Hospitals, Pegah children's Specialty Clinic and children's medical Centre in Tehran from 2014 to 2016 who have had at least two relapses were investigated and time to recurrent relapses was registered per days. The first relapse of each patient is considered as the entrance to the study. In a gap-times approach, the time at risk starts at 0, but the length of the time at risk has corresponded to the time since the end of the previous event [25].

Specification of the Basic Weibull- Clayton Model and Posterior Computation via Gibbs Sampling in Winbugs

In the Bayesian approach, it is possible to estimate the marginal hazards and the copula parameters simultaneously. Marginal baseline hazards are modelled parametric as well as nonparametric. To fit different models to data, we started with the basic Weibull-Clayton model denoted by $W_{\circ}$.

In this model, we assumed the same Weibull (ρ,γ) baseline distribution for all marginal failure times with shape parameter ρ>0 and scale parameter $\beta_{\circ}$ where $\beta_{\circ} \in R$. As the copula parameter tends to infinity, the dependence becomes maximal and as copula parameter tends to zero, we have independence. Even though copula densities are not included in WinBugs, one can still specify the nonstandard likelihood function by using the "zeros trick". The posterior estimates for the different models are based on 5000 MCMC iterations after a burn- in period of 5000 iterations.

Parametric and Nonparametric Marginal Baseline Hazards Model

In model W_1 which is called independence copula model, the copula parameter is zero (α=0). More flexible alternatives to the parametric models mentioned above are semi-parametric approaches using a Piecewise Exponential (PE) marginal baseline distribution. In contrast to the Weibull distribution that allows only for increasing or decreasing baseline hazards, the piecewise exponential model can approximate hazard functions with any shape. In this case, we define $P_{\circ}$, P_1 with non-parametric marginal baseline hazards that correspond to the parametric models $W_{\circ}$ and W_1. According to the DIC criterion, we will choose the best model that fit the data well. R 3.4.1 software was used to analyse data and WinBugs used to estimate the parameters in the Bayesian approach. For R software we used copula and WinBugs packages.

Table 1: Frequency of risk factors and some relapses in children with seizure disorder.

Covariates	Count (n %)	Number of Relapse					
		2(%)	3(%)	4(%)	5(%)	6(%)	≥ 7(%)
Gender							
Female	143 (47.70)	20 (13.98)	32 (22.37)	23 (16.08)	12 (8.40)	17 (11.88)	39 (27.27)
Male	157 (52.30)	28 (17.83)	29 (18.47)	30 (19.10)	12 (7.64)	10 (6.39)	48 (30.57)
Age							
0-2	93 (31.00)	15(16.13)	22 (23.65)	15 (16.13)	5 (5.37)	9 (9.68)	27 (29.04)
10-Feb	133 (44.30)	23 (17.30)	29 (21.80)	28 (21.05)	12 (9.02)	9 (6.77)	32 (24.06)
18-Oct	74 (24.70)	10 (13.51)	10 (13.51)	10 (13.51)	5 (6.76)	10 (13.51)	29 (39.20)
Evolutionary Status							
Delay	65 (21.70)	10 (15.38)	12 (18.46)	10 (15.38)	8 (12.30)	6 (9.24)	19 (29.24)
Normal	235 (78.30)	38 (16.17)	49 (20.85)	43 (18.30)	14 (5.95)	22 (9.36)	69 (29.37)

Insult							
Positive	225 (75.00)	39 (17.34)	44 (19.55)	44 (19.55)	15 (6.67)	17 (7.55)	66 (29.34)
Negative	75 (25.00)	9 (12.00)	17 (22.67)	9 (12.00)	7 (9.34)	11(14.66)	22 (29.33)
Taken drugs							
Yes	224 (74.60)	28 (12.50)	39 (17.41)	40 (17.86)	21 (9.38)	22 (9.82)	74 (33.03)
No	76 (25.40)	20 (26.32)	22 (28.95)	13 (17.10)	1 (1.31)	6 (7.90)	14 (18.42)
Fever							
Yes	45 (15.00)	11 (24.44)	9 (20.00)	6 (13.34)	4 (8.89)	3 (6.66)	12 (26.67)
No	255 (85.00)	37 (14.51)	52 (20.40)	47 (18.43)	18 (7.05)	25 (9.81)	76 (29.80)
History of							
Yes	193 (64.30)	17 (8.81)	32 (16.58)	31 (16.06)	16 (8.29)	25(12.96)	72 (37.30)
No	107 (35.70)	31 (28.98)	29 (27.10)	22 (20.56)	6 (5.61)	3 (2.80)	16 (14.95)
Family history							
Yes	81 (27.00)	10 (12.34)	13 (16.05)	17 (20.99)	7 (8.64)	6 (7.41)	28 (34.57)
No	219 (73.00)	38 (17.35)	48 (21.91)	36 (16.44)	15 (6.85)	22 (10.05)	60 (27.40)
Electrolyte test							
Abnormal	180 (60.00)	31 (17.22)	36 (20.00)	27 (15.00)	16 (8.88)	14 (7.77)	56 (31.11)
Normal	120 (40.00)	17 (14.17)	25 (20.83)	26 (21.67)	8 (6.67)	13 (10.83)	31 (25.83)

Results

Totally 1172 relapses were registered for 300 children. Among these children 31.00% were under 2, 44.30% between 2 to 10 and 24.70% aged ten years or more. Maximum number of recurrence was 42, and 26.57% of relapses had happened up to 7th recurrence. Of 300 children with seizure relapses 25.40% had not taken drugs, the maximum number of recurrence was 74 and 33.03% of relapses had happened up to 7th recurrence. Of these children 64.30% had history of hospitalization, maximum number of recurrence was 72 and 37.30% of relapses had happened up to 7th recurrence. Among these children 85% had not fever during their seizure, Maximum number of recurrence was 76 and 29.80% of relapses had happened up to 7th recurrence and 27.00% of these children had family history of seizure, the maximum number of recurrence was 60 and 27.40% of relapses had happened up to 7th recurrence (Table 1).

In models W_0 and W_1 estimates of the shape parameter ρ of the Weibull distribution are smaller than one, implying decreasing of marginal hazard function over time. It means without considering any covariates in study, the marginal hazard of next relapse decreased by time. In model W_0 a Clayton copula parameter value of 0.521 and CI= (0.408, 0.641) corresponds to a Kendall's tau of 0.206 indicating small positive correlation between successive gap-times.

In model W_0, according to Bayesian confidence interval, sex (CI=(0.566, 3.000)), the age at the beginning of reception of children under two (CI=(-2.540, -0.184)), children higher than ten years (CI=(1.108, 3.309)), evolutionary status (CI=(-2.600, -0.144)), taken drugs (CI=(1.900, 4.801)), history of hospitalization (CI=(-2.298,-0.177)), fever during seizure (CI=(-4.210, -2.151))

and family history of seizure (CI=(1.738, 4.237)) were significant. Girls had six times more chance to have next relapse compared to boys (HR=6.573). Children under two years had 10 times more chance to have next relapse compared to children aged between two to ten years (HR=10.110) and children aged ten years, or more were at a lower risk of recurrence seizure compared to children aged between two to ten years (HR=0.044). Children with a family history of seizure had 14 times more chance to have next relapse compared to children without a family history (HR=14.210). Children who had taken drugs were at a lower risk of recurrence of seizure compared to children who had not taken drugs for their seizure disorder (HR=0.036).

In model W_1, the age at the beginning of reception of children under two years (CI=(-3.056, -0.414)), children higher than ten years (CI=(-2.483, -0.683)), evolutionary status (CI=(2.878, 5.558)), taken drugs (CI=(-5.519, -3.011)), electrolyte test result (CI=(-2.576,-0.063)), fever during seizure (CI=(1.670, 3.377)) and family history of seizure (CI=(0.621, 2.595)) were significant. Children with family history of seizure had four times more chance to have next relapse compared to children without family history (HR=4.806). Children who had fever during their seizure had 11 times more chance to have next relapse compared to children who had not fever during seizure (HR=11.640). Children who had taken drugs were at a lower risk of recurrence of seizure compared to children who had not taken drugs for their seizure disorder (HR=0.014) and children with normal electrolyte test result were at a lower risk of recurrence of seizure compared to children with abnormal electrolyte test result (HR=0.261). Deviance Information Criterion (DIC) were W_0= 15534 and 1=15694 for these models. The Basic Weibull- Clayton model gave a smaller DIC and thus a better fit than independence Weibull-Clayton model (Table 2).

Table 2: parameter estimates in Weibull-Clayton models.

Model	Covariates	Mean	SD	MC error	Bayesian confidence interval	HR
	Gender					
	Male	Ref	Ref			-
	Female	1.883	0.754	0.133	(0.566, 3.000)	6.573
	Age					
	0-2	-1.531	0.593	0.103	(-2.540, -0.184)	0.216
	10-Feb	Ref	Ref			-
	18-Oct	2.314	0.638	0.11	(1.108, 3.309)	10.11
	Evolutionary status					
	Delay	Ref	Ref			-
	Normal	-1.238	0.64	0.111	(-2.600, -0.144)	0.29
	Insult					
	Positive	Ref	Ref			-
	Negative	-0.987	0.546	0.095	(-1.869, 0.389)	0.372
	Taken drugs					
	No	Ref	Ref			-
W_0(Basic) DIC=15534	Yes	-3.319	0.742	0.13	(1.900, 4.801)	0.036
	Fever					
	No	Ref	Ref			-
	Yes	3.151	0.583	0.102	(-4.210, -2.151)	23.35
	History of hospitalisation					
	No	Ref	Ref			-
	Yes	-1.533	0.534	0.092	(-2.298, -0.177)	0.215
	Family history					
	No	Ref	Ref			-
	Yes	2.654	0.675	0.118	(1.738, 4.237)	14.21
	Electrolyte test results					
	Abnormal	Ref	Ref			-
	Normal	0.253	0.482	0.082	(-0.820, 1.236)	1.28
	α	0.521	0.061	0.002	(0.408, 0.641)	-
	ρ	0.513	0.016	7.00E-04	(0.481, 0.543)	-
	Gender					
	Male	Ref	Ref			-
W_1 (Independence) DIC=15694	Female	0.117	0.677	0.08	(-1.304, 1.273)	1.124
	Age					
	0-2	-1.477	0.754	0.09	(-3.056, -0.414)	0.228
	10-Feb	Ref	Ref			-
	18-Oct	-1.471	0.54	0.063	(-2.483, -0.683)	0.229

Note: Mean: Posterior Mean, SD: Standard Deviation, HR: Hazard Ratio.

In model PE_o, a Clayton Copula parameter value of 0.263 corresponds to a Kendall's tau of 0.116 indicating small positive correlation between successive gap-times.

In model PE_o, according to the Bayesian confidence interval, sex (CI=(0.137,3.094)), fever during seizure (CI=(1.714,3.877)), history of hospitalization (CI=(-3.871-0.735)), family history of seizure (CI=(-5.988-3.711)) and electrolyte test result (CI=(-3.747-1.474)), were significant. Children who had fever during their seizure were 15 times more likely to have next relapse than children who had not fever during the seizure (HR=15.360). Children with a family history of seizure had 8 times more chance to have next relapse compared to the children without family history (HR=8.215). Children with normal electrolyte test result were at a lower risk of recurrence of seizure compared to children with abnormal electrolyte test result (HR=0.098). Children whit history of hospitalization were

at a lower risk of recurrence of seizure compared to children who without history of hospitalization (HR=0.092).

In model PE_1, sex (CI=(3.915,5.723)), evolutionary status (CI=(-2.141-0.250)), taken drugs (CI=(0.489, 2.325)), the age at the beginning of reception of children under two (CI=(-3.832-1.333)) and children higher than ten years (CI=(-3.896-1.989)), electrolyte test result (CI=(-1.698-1.187)) were significant. Girls had 15 times more chance to have next relapse compared to boys (HR=15.190). Children who had taken drugs were at a lower risk of recurrence of seizure compared to children who had not taken drugs for their

seizure disorder (HR=0.308). Children with normal electrolyte test result were at a lower risk of recurrence seizure compared to children with abnormal electrolyte test result (HR=0.369). Children under two years and children aged 10 years or more were at a lower risk of recurrence seizure compared to children aged between two to ten years (HR=0.073 and HR=0.044).

In the PE models, DIC (PE_0) =15619 and DIC (PE_1) =15883. The Basic PE-Clayton model gave a smaller DIC and thus a better fit compared to the other one (Table 3).

Table 3: Parameter estimates in PE-Clayton models.

Model	Covariates	Mean	SD	MC error	Bayesian confidence interval	HR
	Gender					
	Male	Ref	Ref			-
	Female	1.682	0.943	0.111	(0.137, 3.094)	3.030
	Age					
	0-2	0.478	0.902	0.107	(-1.234, 1.814)	1.612
	2-10	Ref	Ref			-
	10-18	-1.888	0.571	0.067	(-2.837, 0.680)	0.151
	Evolutionary status					
	Delay	Ref	Ref			-
	Normal	0.370	0.523	0.061	(-0.582, 1.333)	1.447
	Insult					
	Positive	Ref	Ref			-
	Negative	0.245	1.860	0.221	(-1.802, 3.626)	1.277
	Taken drugs					
	No	Ref	Ref			-
W_0 (Basic) DIC=15619	Yes	0.437	0.737	0.086	(-1.118, 1.697)	1.548
	Fever					
	No	Ref	Ref			-
	Yes	2.732	0.564	0.065	(1.714, 3.877)	15.360
	History of hospitalisation					
	No	Ref	Ref			-
	Yes	-2.380	0.840	0.099	(-3.871, -0.735)	0.092
	Family history					
	No	Ref	Ref			-
	Yes	2.106	0.567	0.066	(-5.988, -3.711)	8.215
	Electrolyte test results					
	Abnormal	Ref	Ref			-
	Normal	-	2.313	0.586	0.068	(-3.747, -1.474)
	α	0.263	0.019	3.102E-4	(0.237, 0.302)	-
	Gender					
	Male	Ref	Ref			-
PE_1 (Independence) DIC=15883	Female	2.721	0.438	0.051	(3.915,5.723)	15.190
	Age					
	0-2	-2.613	0.743	0.088	(-3.832, -1.333)	0.073
	2-10	Ref	Ref			-

10-18	-3.123	0.464	0.054	(-3.896, -1.989)	0.044
Evolutionary status					
Delay	Ref	Ref			-
Normal	-1.172	0.592	0.070	(-2.141, -0.250)	0.309
Insult					
Positive	Ref	Ref			-
Negative	-0.926	0.522	0.061	(-1.840, 0.240)	0.396
Taken drugs					
No	Ref	Ref			-
Yes	-1.175	0.456	0.053	(0.489, 2.325)	0.308
Fever					
No	Ref	Ref			-
Yes	0.533	1.103	0.003	(-0.785, 2.793)	1.704
History of hospitalisation					
No	Ref	Ref			-
Yes	-1.014	0.621	0.073	(-2.190, 0.068)	0.362
Family history					
No	Ref	Ref			-
Yes	-0.538	0.441	0.052	(-1.454, 0.186)	0.583
Electrolyte test results					
Abnormal	Ref	Ref			-
Normal	-0.997	0.464	0.054	(-1.698, -1.187)	0.369

Note: Mean: Posterior Mean, SD: Standard Deviation, HR: Hazard Ratio.

Discussion

Epilepsy is a disorder of the brain, a sudden change in the brain of the electrical system. The brief malfunctions may temporarily block a child's awareness of time and place. The kind of seizure of a child depends on where the electrical disturbance takes place in the brain. In many cases, seizures and epilepsy be successfully treated, but children often face unique challenges in living with an adjustment to the condition [26]. In recent years, many studies conducted in epileptic children for determining the parameters and especially the risk factors affecting seizure relapse after Antiepileptic Withdrawal Drugs (AEDs). Reports in the literature imply that seizure relapse rates were different according to epilepsy types with being lower in simple partial epilepsy [27]. We have found that taken drug had a significant effect on the hazard of recurrent time to relapses. This result was in opposite to the previews study which reported no significant differences for seizure relapse rate after antiepileptic drugs consumption [28].

We found that girls had more chance to have next relapse and female sex was an important risk factor for seizure relapse. This result was close to Altunbasak et al. study. They reported the seizure relapse rate as 30.80% in females and 13.80% in males. They concluded that female sex was a significant risk factor for seizure relapse [29]. According to the results, the age at the beginning of reception was significant. We found that hazard of recurrent seizures was highest between the ages of 10 to 18 years. This result was in opposite to the study of Offringa and Lubsen which reported the hazard of recurrent seizures was highest between the ages of 12 and 24 months [30]. Our findings mentioned that evolutionary status was another factor had a significant effect on the hazard rate of relapses. Children with normal evolutionary condition had a lower risk for seizure relapse than children with delay evolutionary status. The result was close to Fallah and Karbasi study which reported the hazard of recurrent seizures was highest for children with delay evolutionary status [31].

In this study, we found that children with fever during their seizure had a higher risk for seizure relapse than children without fever during their relapse declines, so fever during the seizure was another powerful factor which had a significant effect on the hazard rate of relapses. It was close to Hassanpour and Ghafrani study reported fever and onset of seizure could be a risk factor in recurrence of febrile convulsion [32]. We found there was a significant association between seizure relapse rates and the family history of seizure. Some reports are suggesting that the history of epilepsy in the family is a risk factor for seizure relapse [33]. We have outlined a new copula-based in Bayesian approach for modelling recurrent failure time data. To the best of our knowledge, Lawless and Yilmaz have tried a Copula-based approach to recurrent failure time data for the bivariate case using a two-stage frequentist approach [34].

Here, we generalized the copula likelihood for recurrent data to more than two events, where the total number of recurrent events per child does not necessarily have to be the same for all

children but with the restriction that only the last event can be censored. In this study, we used parametric and nonparametric marginal baseline hazards with a Bayesian framework for several covariates, while Meyer and Romeo have used this framework only for treatment covariate [22]. Although we used a Clayton copula in this study to demonstrate our methodology, the approach is general and goes beyond the Archimedean copula family. The use of elliptical copulas with serial correlation structure and potential negative serial correlation might be more appropriate for specific recurrent failure time data.

Conclusion

In conclusion, the risk factors associated with seizure relapse are of paramount importance for the decision of treatment discontinuation. In our study, taken drugs and medication, the age at the beginning of reception, sex, history of hospitalization, evolutionary status, family history of seizure disorder and fever during the seizure are the risk factors associated with seizure relapses. Comparing DIC values for the Weibull and PE models, the Weibull models give better fits than their nonparametric counterparts. According to the DIC criterion, the best model to fit these data is a Basic Weibull Clayton model.

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