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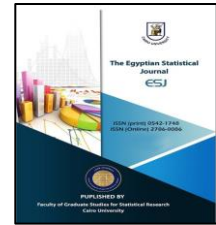
Survival models including excess hazard model and multilevel excess hazard model with application

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Keywords	Abstract
Survival analysis; excess hazard model; multilevel excess hazard model; AIC; BIC.	This paper presents a comprehensive analysis of procedures for the excess hazard model. A common issue with hazard models is estimating the overall hazard rather than the excess hazard, leading to inaccurate parameter estimates. The paper suggests applying various survival models, including the excess hazard model and the multilevel excess hazard model, to enhance the accuracy and reliability of the results. The primary objective of this study is to estimate the excess hazard for both models and conduct a comparative analysis between them. Two statistical criteria, Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), were utilized to evaluate model accuracy. All calculations were performed using the R software system, specifically R version 4.2.2. The multilevel excess hazard model demonstrated superior performance in terms of AIC and BIC compared to the excess hazard model.

1. Introduction

Survival analysis is a statistical branch determining the expected duration until an event occurs, such as death in biological organisms or failure in mechanical systems. It is also termed reliability theory in engineering, duration analysis in economics, and event history analysis in sociology. Survival analysis comprises a set of longitudinal methods for analyzing data with time-to-event outcomes. These events include death, heart attacks, and product expiration, each representing different event types. The Kaplan-Meier estimator is a statistical tool used for estimating survival probabilities.

Additionally, two significant methods in survival analysis are shared frailty models and the Cox proportional hazards model (PHM). Shared frailty models introduce random effects at the cluster level to address observed heterogeneity among clusters, assuming that individuals within the same cluster share identical frailty, thus accounting for the correlation in individual event times. In contrast, the Cox PHM employs a regression approach to analyze proportional hazards. (Streib and Dehmer, 2019).

The fitting of parametric survival models, which follow a normal distribution with random effects, was first introduced by (Prinja et al., 2010). These models were developed to assess overall survival. However, when the primary goal of certain studies is to calculate net survival for

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population comparisons, it implies that the analysis is centered on the likelihood of patients dying solely from the disease of interest, as described by (Lepeule et al., 2006). Net survival indicates that the event's occurrence is the study's focal point, as noted by (Nelson et al., 2007). Two principal frameworks are used to determine net survival: the relative survival setting and the cause-specific setting. The cause-specific setting necessitates information about the event of interest, with all other events being censored, which contrasts with the relative survival setting, as discussed by (Rondeau et al., 2012). Net survival is a robust foundation in both settings due to informative censoring. According to Crowther and Lambert (2014), informative censoring occurs when patients are removed from the risk set in a non-informative manner. In the cause-specific setting, where the primary goal is to estimate the hazard of the main disease, patients who die from causes unrelated to the main disease are censored and thus removed from the risk set. This implies that patients at higher risk of dying from other causes are more likely to be excluded from the risk set. The concept of informative censoring in the relative survival setting is more complex because any variable affecting both disease-specific and other-cause mortality hazards constitutes informative censoring. Goethals et al. (2008) introduced a new estimator to address this within the relative survival framework.

The estimation of net survival is unbiased if informative censoring is accounted for. Nonetheless, biases related to the data set itself may still occur. In the relative survival setting, bias can arise from the lack of comparability between the cohort and the general population, from which expected mortality rates are derived, due to unmeasured variables (S) affecting both expected and excess hazard rates. Additionally, in the cause-specific setting, bias can result from the misclassification of the underlying cause of death (Bower et al., 2016). The remainder of this paper is structured as follows: Section 2 presents the model specifications, Section 3 discusses the estimation methods, Section 4 provides a numerical analysis, and Section 5 concludes with a general discussion and potential extensions of our application.

2. Model Specification
2.1 Excess Hazard Model

The excess hazard model is a regression model utilized to analyze disease registry data for estimating net survival, particularly when the disease being studied is the primary cause of death. There are several frameworks for analyzing survival data. The first is the overall survival framework, where mortality from all causes is analyzed. The second is the cause-specific framework, which requires information on various causes of death. The third type is the relative survival framework, which applies when information on the cause of death is unavailable. The key concept of this framework is to segregate the hazard attributable to other causes of death from the hazard associated with the disease of interest. Assuming an additive decomposition of the individual hazard function, $h(.)$, into two components: the first, $h_{ou}(.)$, is the hazard related to other causes of death, and the second, $h(.)$, pertains to the hazard from the main cause of death under study (Austin, 2017; Jenkins, 2008). Here, λ_{oth} represents the expected hazard while λ_p denotes the population hazard, was estimated based on demographic characteristics encapsulated in the vector (Z) (such as age, sex, etc.) using population life tables. This approach is adopted in conjunction with the hazard of mortality from the disease of primary interest in the study (Gasparini et al., 2019).

$$\lambda(t, a, x, z) = \lambda_+(t.x) + \lambda(a + t, z) \qquad (1)$$

Where:

t: The time since diagnosis.

a: The diagnosis age.

$a + t$: The censoring age or death.

X: The prognostic covariates vector.

z: A vector of population characteristics.

We can define the excess hazard as follows:
- The logarithm of the baseline excess hazard λ modeled by a B-spline time function.
- Non-linearity of covariates effect by introducing an adequate B-spline covariates functions.
- Non-proportionality is modeled in terms of interaction terms between the covariates and a B-spline time function.

To formulate the three covariates effect, **X₁:** was a linear proportional effect of the axes hazard logarithms. **X₂:** a continuous variable with a non-linear proportional effect, and **X₃:** were the effects of a non-proportional (time-dependent).

Numerous studies, such as those by (Goungounga, et al., 2023; Eletti, et al., 2022 and Crowther, et al., 2019), have engaged in extensive discussions regarding the placement of spline knots in survival models. A widely accepted practice for selecting knot locations is to use the percentiles of the uncensored survival time distribution. Drawing on prior knowledge, we can define the knots accordingly.

2.2 Multilevel Excess Hazard Models

Multilevel models address hierarchical structures by introducing a random effect for each cluster, thus providing an appropriate theoretical framework for estimating net survival. Clustered data are frequently observed in various settings. In the medical field, the analysis of recurrent event data is a typical example, where patients may experience the event of primary interest multiple times during the follow-up period (Amaral et al., 2024). To account for confounders and incorporate non-proportional hazards in covariate effects, the data are analyzed simultaneously, considering the hierarchical structure of individuals (Prinja et al., 2010). Often, we analyze the effect of a random treatment. First, we introduce some concepts for each individual for $(j, j = 1,2.....n_i)$. from cluster (i) (which could be a geographical unit, with i, $(i = 1.2...D)$. Let t_{ij} represent the observed time-to-event, and let δ_{ij};) be the censoring indicator, which takes the value of one if an event occurred and zero if censoring occurred. The model is structured as follows:

$$\delta_{ij} = \begin{cases} 1, & case\ of\ event, \\ 0, & case\ of\ censoring. \end{cases} \tag{2}$$

We can define the multilevel excess hazard effect model as follows- :

$$\lambda(t, X_{ij}, Z_{ij}, \omega_i) = \lambda_+(t, X_{ij},)exp(\omega_i) + \lambda_p(t + a, Z_{ij}) \tag{3}$$

Where:
w_i: The cluster level of a random effect.
$u = exp(\omega)$: The shared frailty of assumed distribution.

3. Estimation Methods

To model frailty parameters, various studies have employed a gamma distribution because the method of likelihood estimation allows for an approximate expression in this scenario (Belot et al., 2023). This approach is particularly feasible in excess hazard models due to the division of the total hazard into the excess hazard and the population hazard. Consequently, estimating the likelihood in this context necessitates a numerical integration step, also known as quadrature. Nonetheless, a gamma distribution can be adapted for excess hazard models using the quadrature method. Despite this, the preference for this distribution is often avoided. To streamline the model estimation process, alternative distributions, such as the normal distribution for the random effect (w), with a mean of zero and a variance that follows a log-normal distribution, are considered. Shared frailty can be estimated through numerical integration.

3.1 Maximum likelihood estimation

The estimators of the maximum likelihood are used to get the estimation of excess hazard. Suppose a single observation known as (t_{ij}, δ_{ij}) from cluster i depended on the random effect value, the likelihood can be written as follows-:

$$L_{ij}^c(\beta|\omega_i) = (\lambda_+(t_{ij}, X_{ij}, \omega_i) + \lambda_p(t_{ij} + a, Z_{ij}))^{\delta_{ij}} S(t_{ij}, X_{ij}, \omega_i). \tag{4}$$

The parameters of the baseline hazard and the effect of covariates can be re-grouped in one vector called β and

$$S(t_{ij}, X_{ij}, \omega_i) = exp((-\Lambda_+(t_{ij}, X_{ij}, \omega_i) - \Lambda_p(t_{ij} + a, Z_{ij})). \tag{5}$$

Where:
Λ_+ :-Represents the cumulative excess hazard
Λ_p:- Population cumulative excess hazard introduced by the general formula:-

$$\Lambda(t) = \int_0^t \lambda(u)du. \tag{6}$$

In practice, the latter exponential terms of the previous formula were deleted from the estimation process because it does not rely on the estimated parameters. For cluster, i the conditional likelihood is defined as:

$$L_i^c(\beta|\omega_i) = \prod_{i=1}^{n_i}(L_{ij}^c(\beta|\omega_i)) \tag{7}$$

Then, obtaining the effect of marginal likelihood t for cluster i by integrating the conditional likelihood through the random effect distribution:

$$L_i^M(\beta|\sigma) = \frac{1}{\sigma\sqrt{2\pi}}\int_{-\infty}^{\infty} L_i^c(\beta|\omega_i)\exp\left(\frac{\omega^2}{2\sigma^2}\right)d\omega \tag{8}$$

The estimation of model parameters (β, σ) using the full log-likelihood function can be written as:

$$l(\beta|\sigma) = \sum_{i=1}^{D}\log\left(L_i^M(\beta|\sigma)\right) \tag{9}$$

The algorithm of this method is as follows (Kim, J. S., 2003):-

a) Maximize $l(\beta^{(k)}, \lambda)$ with respect to λ to get $\lambda^{(k)}$.

b) Maximize $l(\beta, \lambda^{(k)})$ with respect to β, and let $\beta^{(k)}$ be the maximizer at $k \to k + 1$.

c) To get the convergence repeat steps (a) and (b).

3.2 Adaptive Gauss-Hermite quadrature:

This method calculates the log-likelihood function of generalized linear mixed models. The main procedure involves multiplying and integrating the parameter of interest using a carefully chosen probability density function, as described by (Kabaila and Ranathunga 2019). Analytical evaluation of the full log-likelihood is not feasible because the expression for the integration of the cluster-specific marginal likelihood cannot be approximated in a simple form. However, the Gauss-Hermite quadrature allows us to estimate these marginal likelihoods by evaluating the cluster's specific conditional likelihood function at designated points, known as quadrature nodes. For cluster k, we have:

$$\frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\infty} L_i^c(\beta|\omega_i) \exp\left(\frac{\omega^2}{2\sigma^2}\right) d\omega \; \propto \; \sum_{i=1}^{Q} \rho_i L_k^c(\beta|a_i) \tag{10}$$

Where:
a_i : are the nodes.
ρ_i: are the weights.
These parameters are determined from the zeros of a polynomial of the Q-th order Hermite. These nodes are independent of the conditional likelihood function L_k^c implying that the locations of the nodes may not fully capture the regions of maximal variation in L_k^c, as expressed in:

* Integration with low estimation.
* Using a large node number to improve this estimation.

Therefore, the main idea of this approximate method is to devise a new quadrature formula incorporating these nodes and their associated weights into the integrand by transforming the integration. Then, the nodes are rescaled to encompass regions where the integrand varies more. To approximate the integral around its nodes, the method relies on the Laplace method and the estimation of adaptive Gauss-Hermite quadrature, which corresponds to the standard Laplace approximation for integrals of positive functions, as outlined by Jin and Andersson (2020). For a small number of quadrature points, adaptive Gauss-Hermite quadrature provides a better approximation of the integral. This improvement stems from the transformation of nodes and their corresponding weights, which allows for speculating the integral for each cluster's logarithmic first and second derivatives, as discussed by Stringer and Bilodeau (2022).

4. Numerical Analysis

This study relied on a simulated dataset obtained from an R package. The independent variables in the dataset include Age, Depindex, Sex, ID cluster number, Time of follow-up, and vital status. The dependent variable is the popmrate variable, representing the population (expected) mortality rate at the time of censoring. Descriptions of these variables will be provided in the following:

Table 1 presents the simulated dataset obtained from R packages. This dataset comprises 4000 rows and 8 columns, with each variable having 4000 observations. The analysis of this data relied on specific packages such as **mexhaz** and **psych**, which were utilized for data analysis.

Table 1: Descriptive of Variables of Simulated Data Variables

Variable	Description
Age	Age at diagnosis (continuous).
Depindex	Deprivation index (continuous).
IsexH	Sex (0 = Female, 1 = Male).
Clust	ID number of the cluster.
Vstat	Vital status (0 = Alive, 1 = Dead).
Timesurv	Follow-up time (years).

Table 2 presents the descriptive statistics of the quantitative variables. The results indicate that depindex has the lowest standard deviation, with a value of 1.18. This suggests that a variable exhibits less variation among its observations than the other variables. Following depindex, the variable of time survival shows the next lowest standard deviation, followed by the variable of age.

Table 2: Descriptive Statistics for Simulated Variables of Quantitative Data

Variable	n	Min	Max	Mean	S.D
Age	4000	30.3	84.96	68.49	13.72
Depindex	4000	-2.79	2.78	0.02	1.18
Clust	4000	1	50	25.5	14.43
Time Survival	4000	0	10	3.61	3.78

Table 3 provides the descriptive statistics of the categorical variables sex and vital status, including each variable's frequency, percentage, and cumulative percentage. The previous table revealed that the percentage of deaths is higher than the percentage of individuals who are alive. This highlights the impact of independent variables on increasing the mortality rate.

Table 3: Descriptive Statistics for Simulated Data Categorical Variables

Variable		Frequency	Percent	Valid Percent	Cumulative Percent
IsexH	Female	2036	50.9	50.9	50.9
	Male	1964	49.1	49.1	100.0
	Total	**4000**	**100.0**	**100.0**	-
Vstat	Alive	763	19.1	19.1	19.1
	Dead	3237	80.9	80.9	100.0
	Total	**4000**	**100.0**	**100.0**	-

Table 4 displays the parameter estimates for the excess hazard model. The results indicate that all parameters affect the vital status. According to the excess hazard model, the variable with the

lowest standard error, implying minimal differences between its units, is the age variable. This suggests convergence among ages in terms of their impact on vital status.

Table 4: The Estimation of Excess Hazard Model Parameters

Parameter	Estimate	StdErr	z.value	p.value
logLambda	-4.6772	0.1365	-34.3	<0.01
logRho	-0.4394	0.0166	-26.5	<0.01
Age	0.0470	0.0018	26	<0.01
Depindex	0.0936	0.0166	5.64	<0.01
IsexH	1.0054	0.0423	23.8	<0.01

Table 5 describes the estimation of multilevel excess hazard model parameters. The previous table showed that explanatory and response variables had a significant relationship. Therefore, all explanatory variables had an influential effect on the rate of mortality.

Table 5: The Estimation of Multilevel Excess Hazard Model Parameters

Parameter	Estimate	StdErr	z.value	p.value
logLambda	-4.7564	0.1431	-33.2348	<0.01
logRho	-0.4236	0.0166	-25.448	<0.0165
Age	0.0478	0.0018	25.9311	<0.01
depindex	0.0944	0.0312	3.0216	<0.01
IsexH	1.0326	0.0434	23.8071	<0.01
Clust	-1.5292	0.1462	-10.4585	<0.01

Table 6 presents the efficiency criteria of the proposed models. The results indicate that the best-performing model, based on these criteria, is the multilevel excess hazard model with 6 degrees of freedom and 50 clusters. The log-likelihood value for this model is -5739.7. These findings provide evidence of a negative relationship between the independent variables and the risk of death.

Table 6: Efficiency Criteria

Model	log-likelihood	Df	AIC	BIC
Excess hazard model	-5765.1	5	11540.18	11571.65
Multilevel excess hazard model	-5739.7	6	11489.43	11520.9

Table 7 presents each model's parameter estimates at different sample sizes, along with the standard errors of the parameters and comparison criteria used to determine the best model. From the analysis of this table, several key findings emerge:

First: There exists a negative relationship between the explanatory variables and the dependent variable.

Second: The standard error of log lambda for the multilevel excess hazard model is greater than that of the excess hazard model. This is likely due to the multilevel model's differences between levels and clusters.

Third: Regarding efficiency criteria, the best model fit is observed for the multilevel excess hazard model at a sample size of n=25.

Table 7: Bootstrap Estimation Method and Criteria of Comparison between Models.

Model	Parameter	n=25	n=50	n=100	n=200
Excess hazard model		-5.337	-5.0	-4.8	-4.7
Multilevel excess hazard model	log lambda	-6.503	-5.3	-5.0	-4.9
		n=25	n=50	n=100	n=200
Excess hazard model	Std. error log lambda	2.211	1.3	0.9	0.6
Multilevel excess hazard model		3.182	1.6	1.0	0.7
Model	**Criteria**	**n=25**	**n=50**	**n=100**	**n=200**
Excess hazard model	AIC	75.6	148.6	292.3	581.2
Multilevel excess hazard model		75.1	148.0	291.5	579.9
		n=25	n=50	n=100	n=200
Excess hazard model	BIC	81.7	158.2	305.3	597.7
Multilevel excess hazard model		81.2	157.6	304.5	596.4

Figure 1 illustrates the estimation of log lambda for both models at various sample sizes (n = 25, 50, 100, 200). The figure demonstrates that the estimation of log lambda, representing the hazard parameter, decreases as the sample size increases. Moreover, the multilevel excess hazard model exhibits the greatest rate of decrease in log lambda compared to the excess hazard model. This suggests that as the sample size increases, the hazard parameter tends to decrease more rapidly in the multilevel excess hazard model.
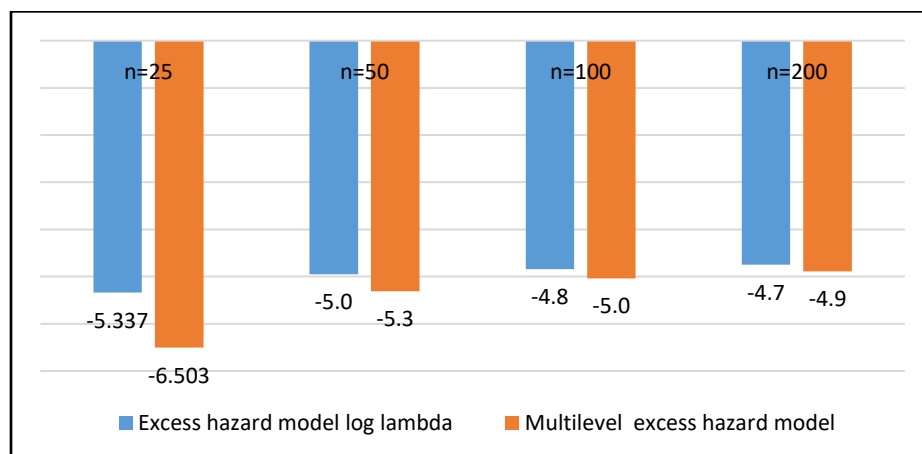

Figure1: log lambda estimation

Figure 2 demonstrates that all three shapes exhibit data symmetry, as indicated by the symmetrical nature of the box plot. The data values are clustered closely around the median, with no outliers present. Additionally, the scatter plot illustrates the close relationship between the variables, indicating a strong correlation between them.
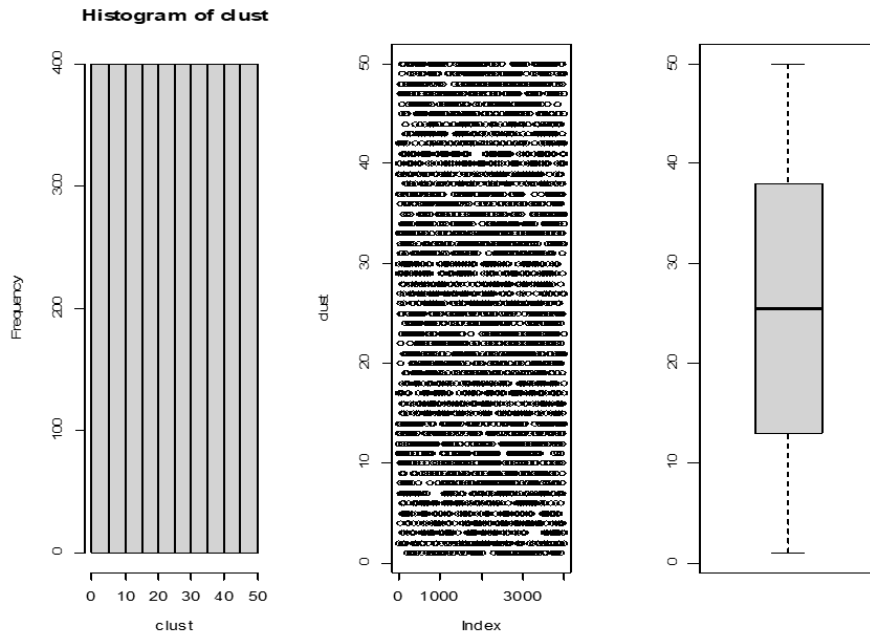

Figure 2: Histogram, Scatter plot, and Box plot of clusters.

Figure 3 displays the standard error of log lambda for both the excess hazard model and the multilevel excess hazard model at various sample sizes. The figure reveals slight variations in the standard error between the two models, which can be attributed to cluster differences.
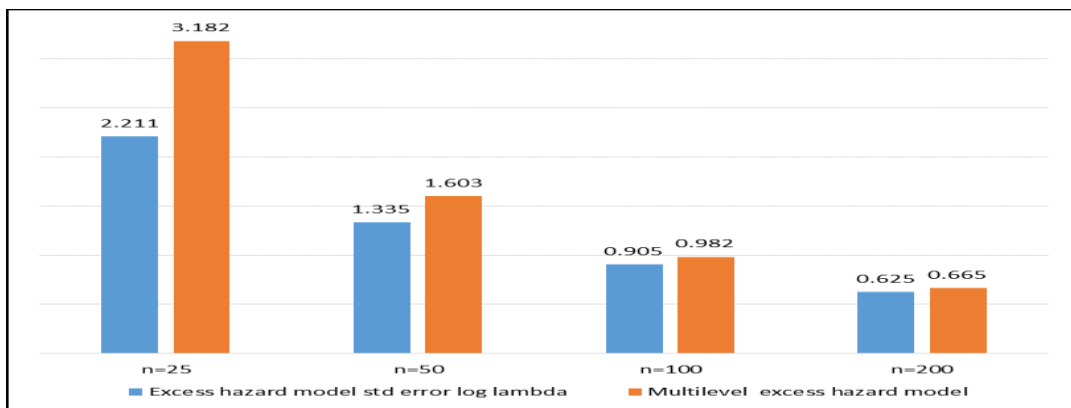
Figure 3: Log lamda standard error.

Figure 4 presents the efficiency criteria of the proposed models at the sample sizes examined in this paper. Based on two criteria, it is evident that the multilevel excess hazard model emerged as the best model.
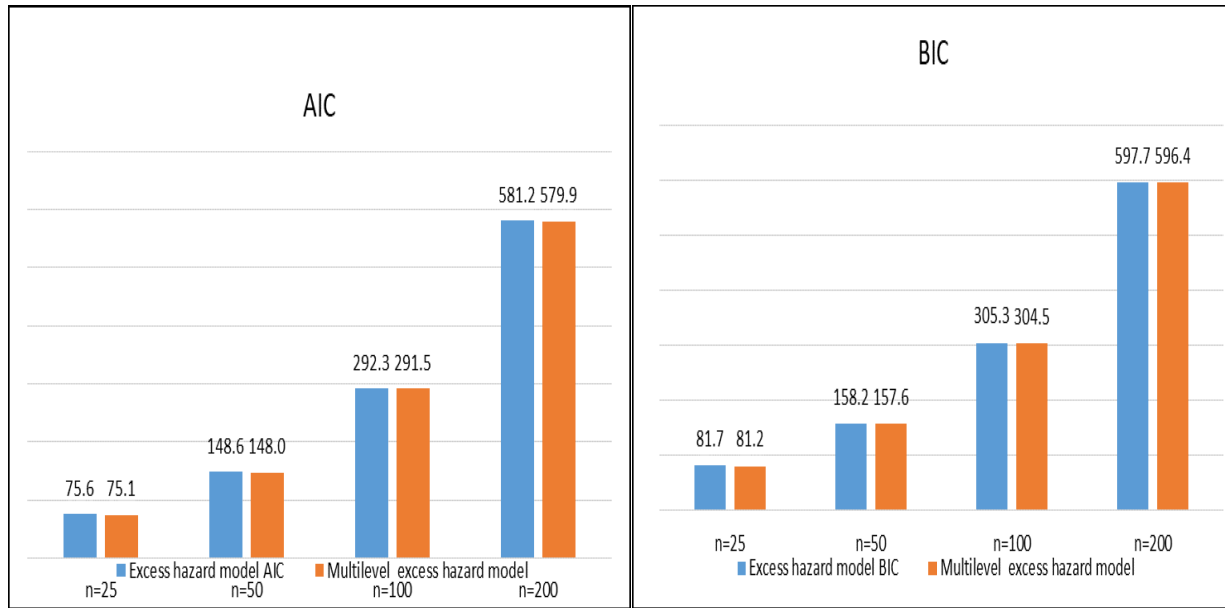
Figure 4: Efficiency criteria

Figures 5 and 6 depict the hazard rate at two age levels (30 and 80), corresponding to mid-age and final age points, respectively, as these points represent the highest hazard rate. These figures demonstrate that as survival time increases, the hazard rate decreases, providing evidence of an inverse relationship between the two variables.
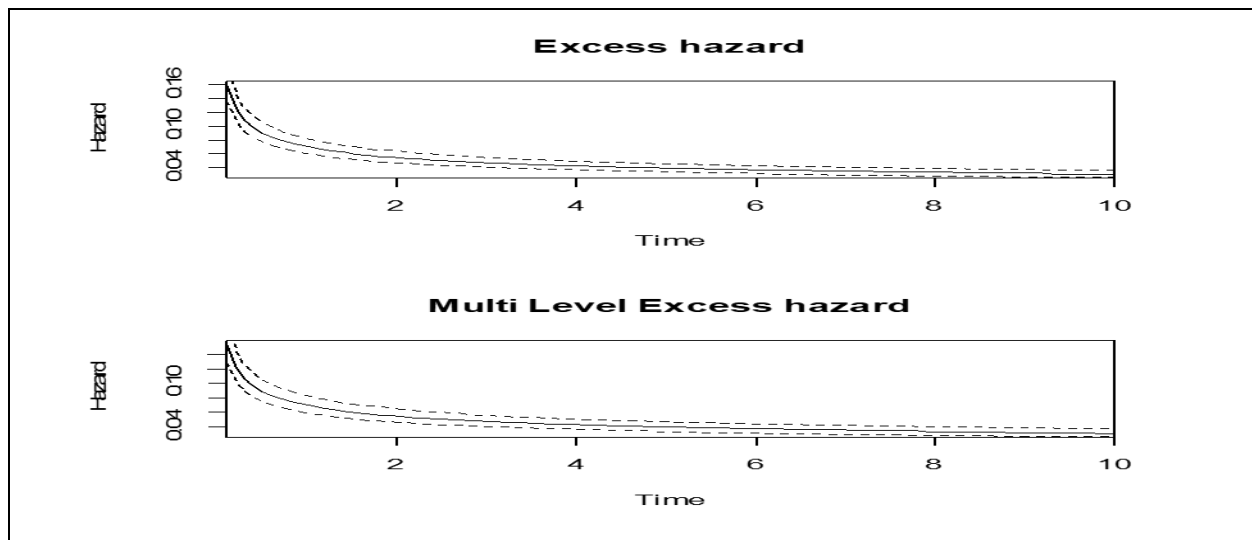

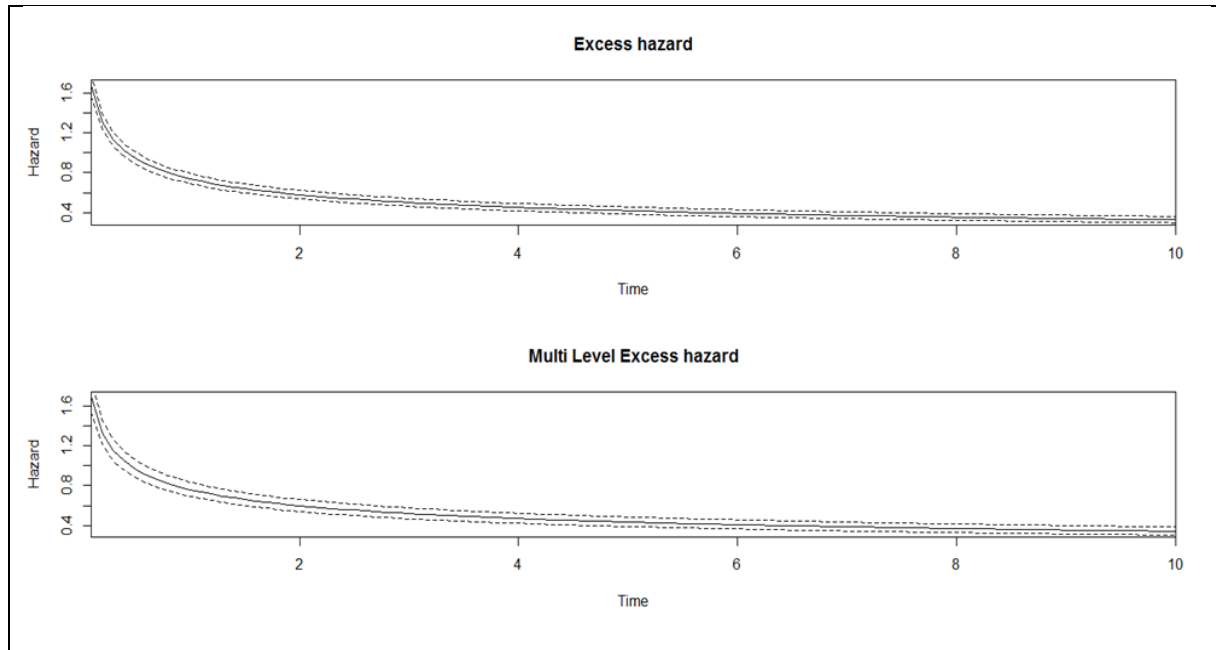Figure 5: Excess hazard and multilevel excess hazard at age 30

Figure 6: Excess hazard and multilevel excess hazard at age 80.

5. Conclusion

In this paper, we introduced two survival analysis models, namely the excess hazard model and the multilevel excess hazard model, to estimate the excess hazard (log lambda). These models were applied to data from the R program to assess the estimation of this parameter. The model parameters were estimated using maximum likelihood and bootstrap estimation methods. Additionally, criteria measurements were conducted at different sample sizes (25, 50, 100, and 200). The multilevel excess hazard model, which included 50 clusters based on real data, was utilized in the analysis. The estimation results revealed a negative relationship between the excess hazard parameter and survival time. Furthermore, the multilevel excess hazard model's hazard was greater than that in the excess hazard model. For efficiency criteria, the multilevel excess hazard model emerged as the best model for both criteria, indicating its superior performance in model fitting.

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