Original Research Article

Application of Multiplicative and Additive Hazards Models to Injury Prevention among Healthcare Workers

ABSTRACT

The Cox multiplicative model is used widely in survival analysis, where the covariates act multiplicatively on unknown baseline hazards. However, the Cox model requires the proportionality assumption, which limits its applications. The additive hazards model has been used as an alternative to the Cox model, where the covariates act additively on unknown baseline hazards. In this study, the performance of the Cox multiplicative hazards model and the additive hazards model has been demonstrated~~, using~~ in an injury prevention study. Both the multiplicative and additive hazards models show~~ed~~ similar results in selecting significant covariates in the final model in our study. The coefficient of the covariates in the additive hazards model is easy to interpret in an additive manner and should be considered when the proportionality assumption of the Cox model is doubtful. The multiplicative and additive hazards models describe different features of the association between the risk factors and the study outcomes. They may be used each other as supplementary approach for further understanding of the data.

Keywords: survival analysis, Cox model, Aalen's ~~multiplicative~~ model, ~~additive~~ Lin & Ying's model, injury ~~prevention~~study, ~~healthcare worker~~occupational health

1. INTRODUCTION

In survival analysis, the Cox hazards model [1] is the most widely used in survival analysis. In this model, the effect of the covariates acts multiplicatively on some unknown baseline hazard. However, when the proportionality assumption is not satisfied, the Cox model can lead to potentially biased estimates and conclusions [2]. Alternatively, additive hazards model has been proposed. The additive hazards model assumes that the covariates act in an additive manner on an unknown baseline hazard. Aalen's additive model as a non-parametric approach specifies how the hazard rate depends on covariates in a linear way and allows one to assess possible changes in the influence of the covariates over time [3]. The estimation procedure for Aalen's model was determined by the cumulative regression functions. By several authors, applications of Aalen's model have been described and further development has been recommended [4-9]. Aalen's approach leads to weighted comparisons of the crude estimate of the hazards rate of each group as compared to a baseline group [10]. This weighting leads to inconsistent tests in the sense that the test statistic depends on which group someone picks as the baseline group.

The Lin and Ying observed that this lack of progress is attributed to the fact that the partial likelihood approach cannot be used directly to eliminate the baseline hazard in estimating the intercept [11, 12]. They have developed procedures with high efficiencies for making inferences about the regression parameters under the additive hazards model with an unspecified baseline hazards function. In their study, a simple semi-parametric estimating function for the intercept was constructed, which imitated the martingale feature of the partial likelihood score function for baseline hazards. In the subsequent

paper, they suggested the semi-parametric analysis of general additive-multiplicative hazard models for the counting process and the additive hazards regression models for survival data but compared these with the frailty model [13]. Others applied the additive hazards model to competing risks setting [14, 15]. Yin and Cai [16] proposed an additive hazard model for multivariate failure time data. Lim and Zhang [17, 18] compared both the additive and multiplicative hazards models in recurrent event data. As an extension, a flexible additive-multiplicative hazard model based on Aalen's and Cox's models have been proposed [19-24]. For additive-multiplicative hazard model, some covariate effects are believed to result in multiplicative effects whereas other effects are best described as additive. However, in practice, it is not easy to decide which covariates to be included additively and which ones to be included multiplicatively. For the additive model, plots of the cumulative regression function provided an appealing explanation for how the hazards profiles were distributed.

2. STUDY DESCRIPTION

Injuries associated with p~~P~~atient handling ~~injuries~~ are common among health care workers and the risk of injury increases with the number of patient handling tasks performed. Studies showed that a transfer, lifting and repositioning (TLR) program may prevent injuries while performing one type of manoeuvre and not another depending on the emphasis of the intervention. To evaluate injuries associated with patient handling ~~patient handling injuries~~ following a multi-factor ergonomic intervention program among health care workers, a quasi-experimental study which had a TLR intervention group and a non-randomized control group was conducted. Descriptions of the overall study design and profile have been published elsewhere [25, 26]. Briefly, this study was conducted in two Health Regions (3 hospitals for the intervention and 3 for the control) in Saskatoon, Canada, from September 2002 to December 2006. The hospitals were matched on hospital type and size. The TLR intervention program component consisted of staff education on anatomy, injuries, body mechanics, personal health, lifting and patient handling procedures, standardized patient handling needs assessment and patient handling algorithms. All direct health care workers, who were employed as such in the

study time periods, were eligible for inclusion into the study. Injuries occurred in lower and upper back, shoulder, neck, extremity, and other body parts were included. The control hospitals had not received any form of injury prevention program during the study period other than standard occupational health and safety practice. Each intervention and control hospital was followed for two year after completion of the intervention program. Gender, age, occupation type, work department, and hospital size were also obtained from the database. The primary outcome was the times to the event of TLR related injury occurring in subjects during the study time. A total of 1,467 subjects were eligible for the study.

With this ~~example~~data set, we use three models (Cox multiplicative hazards model, Aalen's additive hazards model, and Lin & Ying's additive hazards model) ~~(i)~~ to determine which combination of potential explanatory variables affects the form of the hazard function and ~~(ii)~~ to obtain an estimate of the hazard function itself for an individual. We will also examine the goodness-of-fit analysis of the models.

3. MODELS AND METHODS

Within the framework of the multiplicative or additive hazards regression models, a variety of models have been proposed and utilized in real applications. The Cox multiplicative and Lin & Ying's additive hazards models received the greatest attention due to relatively easy interpretation of the covariate effects. These two models assume unspecified baseline hazards and constant covariate effects. In our study, we will assume that all censoring is non-informative and independent, i.e., knowledge of a censoring time for a subject provides no further information about the subject's likelihood of survival at a future time.

3.1. Basic Notations

Suppose that there are n subjects in a study. Let T_i be the time when the event of interest occurs for the ith subject and C_i be the corresponding censoring time. T_i is measured from the subject's study enrollment and the censoring C_i occurs after the subject has been entered into a study to the right of the last known failure time; thus, it is right censoring.

When T_i is subject to right censoring, the failure time X_i is a minimum of (T_i , C_i), i.e., X_i is equal to T_i if the event was observed and is equal to C_i if it is censored. Let δ_i = I($T_i \leq C_i$), where I(.) is an indicator function and takes the value 1 when $T_i \leq C_i$ and is 0 otherwise. Let Z_i be a covariate vector of p-dimensions for the ith subject. The hazard function for the ith subject, $\lambda_i(t)$, is assumed to take either multiplicative or additive forms.

3.2. Multiplicative Hazards Model

The Cox model is one of the most commonly used multiplicative hazards models. The effect of the covariates in the Cox model was to act multiplicatively on some unknown baseline hazards. The model is very useful in practice because either the estimated coefficients themselves or simple functions of them can be used to provide estimates of hazard ratios. In addition, statistical software is readily available, and it is easy to fit models, check model assumptions, and assess model fit.

For Cox proportional hazards model, the hazard function is

$$\lambda\ (t) = \lambda_0 (t)\ e^{\vec{\beta}' \vec{Z}(t)} \qquad (1)$$

where t is the time since a subject's study enrollment. Note that $\lambda_0\,(t)$ are unspecified baseline hazard functions. The corresponding partial likelihood function [2] is

$$L(\vec{\beta}) = \prod_{i=1}^{n} \left\{ \frac{e^{\vec{\beta}' \vec{Z}_i(X_i)}}{\sum_{j=1}^{n} Y_j(t)\ e^{\vec{\beta}' \vec{Z}_j(X_j)}} \right\}^{\delta}, \qquad (2)$$

where $Y_j\,(t) = I\,(X \geq t)$ is a risk set indicator. $\vec{\beta}$ is a p-vector of regression coefficients of Z_i. In order to draw a semi-parametric inference on $\vec{\beta}$ for the model (1), the score functions $U(\vec{\beta})$ are obtained by differentiating the logarithm of $L(\vec{\beta})$ with respect to $\vec{\beta}$. The maximum partial likelihood estimator $\hat{\vec{\beta}}$ is obtained by solving the corresponding

score equation, $\frac{\partial \ln L(\vec{\beta})}{\partial \vec{\beta}} = 0$. The variance-covariance matrix is estimated from the inverse of the information matrix, $I^{-1}(\hat{\vec{\beta}})$.

3.3. Additive Hazards Model

The simple additive hazards model given by Cox and Oakes [27] is

$$h(t|\mathbf{Z}) = h_0(t) + \varphi(\mathbf{Z}) \quad (3)$$

where $\varphi(0)=0$ and $\varphi(\mathbf{Z})$ is constrained so that the right-hand side is non-negative. $h_0(t)$ is the baseline hazard and the covariates act in an additive manner on an unknown baseline hazards rate. Aalen's additive model [3, 28] and Lin and Ying's additive models (L-Y model) [11] have received great attention in the literature. In Aalen's model, the unknown risk coefficients are allowed to be functions of time so that the effect of a covariate may vary over time. The least-squares approach is used to estimate the cumulative regression functions and the standard errors of these functions [29]. In the L-Y model, the time-varying regression coefficients in Aalen's model are replaced by constants and the estimating equation is obtained from the score function to estimate the model. In the next section, these additive hazards models will be reviewed.

3.3.1. Aalen's additive hazards model

In the Aalen's additive hazards model, the covariates are assumed to impact additively upon an unknown baseline hazard, but the effects are not constrained to be constant [28]. Thus, the hazard function under the Aalen's model for the *i*th subject with a *p*-vector of the covariates $Z_i = (z_{i1}, \ldots, z_{ip})$ is defined as:

$$\lambda_i(t) = \lambda_0(t) + \gamma_1(t)\ z_{i1}(t) + \ \ldots\ + \gamma_p(t)\ z_{ip}(t). \quad (14)$$

where $\lambda_0(t)$ is an unspecified baseline hazard function, and coefficient $\gamma_k(t)$ is allowed to vary freely over time, where $k = 1, 2, \ldots, p$. Aalen shows that if a covariate is independent of all the other covariates in the model, then the regression model with this covariate eliminated is the same as the regression model with this covariate included [28]. Note that this fact is not true for the Cox proportional hazards model. The additive effect

$\gamma_k(t)$ may change in magnitude and even sign with time. As it is not straightforward to estimate $\lambda_0(t)$ non-parametrically, direct estimation of the coefficient $\gamma_k(t)$ is difficult. Aalen and others [8, 28] have developed least square estimation of integrated coefficients

$$\Gamma_k(t) = \int_0^t \gamma_k(u)\, du \,. \qquad (5)$$

The usual method of representing the effect $\gamma_k(t)$ is to graph them against time. To define how the effects of covariates changes over the time, cumulative regression function plots estimated by the Aalen's model can be examined. The values of $\gamma_k(t)$, the absolute increase in hazard at time *t*, are not actually observed, but their relative size may be inferred from the slope of the line. The Aalen's plots are obtained by estimating the instantaneous contributions of covariates to the hazard at each distinct failure time and summing up the resulting estimates. The slop of such plots indicates whether a specific covariate has a constant or a time-dependent effect [6]. Slope of an estimated cumulative regression function is positive when covariate increase corresponds to hazard increases, and negative when covariate increases correspond to hazard decrease. Cumulative-sums slop approaches zero when a covariate has no effect on the hazard.

3.3.2. Lin & Ying's (L-Y) additive hazards model

We know from Aalen's additive hazards model the conditional hazards rate of a subject, given a set of covariates, and that the regression coefficients are the function of time. Lin and Ying proposed an alternative additive hazards regression model, which is the most closely connected and analogue to the Cox model [11-13]. The L-Y additive hazards model for the *i*th subject with covariate vector $Z_i = (z_{i1}, \ldots, z_{ip})$ is $\lambda_i(t)$, such that

$$\lambda_i(t) = \lambda_0(t) + \gamma_1 z_{i1}(t) + \ldots + \gamma_p z_{ip}(t). \qquad (6)$$

The covariates are assumed to act additively on a baseline hazard $\lambda_0(t)$ and coefficient γ_k is constant additive effects, where $k = 1, 2, \ldots, p$. Lin and Ying [11] propose a heuristic estimation method based on a estimating equation due to the Cox's partial likelihood. Their method successfully treats the baseline hazard as nuisance and removed

them from estimating the regression coefficients. Using the counting process and martingale approach, they obtained closed-form estimators for the regression parameters and the cumulative baseline hazard function.

In order to draw semi-parametric inference on the coefficient $\vec{\gamma}$ for model, the key quantities are given by:

$$\boldsymbol{U} = \sum_{i=1}^{n} \int_{0}^{\tau} [Z_i(t) - \bar{Z}(t)]\, dN_i(t) \qquad (7)$$

$$\boldsymbol{A} = \sum_{i=1}^{n} \int_{0}^{\tau} [Z_i(t) - \bar{Z}(t)]^{\otimes 2}\, Y_i(t)\, dt \qquad (8)$$

$$\boldsymbol{B} = \sum_{i=1}^{n} \int_{0}^{\tau} [Z_i(t) - \bar{Z}(t)]^{\otimes 2}\, dN_i(t) \qquad (9)$$

where, for any vector a, $a^{\otimes 2} = aa^T$; τ is a pre-specified time point usually set to $\max\{ X_1, X_2, \ldots, X_n \}$ such that all observed failures are included in the analysis, and

$$\bar{Z}(t) = \frac{\sum_{i=1}^{n} Y_i(t)\, Z_i(t)}{\sum_{i=1}^{n} Y_i(t)} \sum_{i=1}^{n} Y_i(t) \qquad (10)$$

is the at-risk weight covariate mean at time t. Lin and Ying [11] proposed to estimate $\vec{\gamma}$ by

$$\hat{\vec{\gamma}} = \boldsymbol{A}^{-1}\, \boldsymbol{U}\,, \qquad (11)$$

while the estimated variance of $\vec{\gamma}$ was derived to be:

$$\hat{V}(\hat{\gamma}) = \boldsymbol{A}^{-1}\, \boldsymbol{B}\, \boldsymbol{A}^{-1}\,. \qquad (12)$$

Here, neither $\boldsymbol{A}$ nor $\boldsymbol{B}$ involves the regression parameter. They showed that $\hat{\vec{\gamma}}$ is asymptotically normal with mean $\vec{\gamma}$ and with a variance-covariance matrix consistently estimated by $\hat{V}(\hat{\vec{\gamma}})$. More precisely, $(\boldsymbol{A}^{-1}\, \boldsymbol{B}\, \boldsymbol{A}^{-1})^{-1/2}\, (\hat{\vec{\gamma}} - \vec{\gamma})$ converges in distribution to $N(0, 1)$. The L-Y model has a limitation that the linear predictor $\vec{\gamma}\, Z_i(t)$ needs to

constrained to ensure positivity [13]. One may avoid this constraint by replacing $\vec{\gamma}\ Z_i(t)$ by $e^{\vec{\gamma}Z(t)}$, in which case $\lambda_0(t)$ pertains to the hazard function under $\vec{\gamma}\ Z_i(t) = -\infty$ rather than under $Z_i(t) = 0$.

3.3.3. Model Goodness of Fit

The use of diagnostic procedures for model checking is an essential part of the modeling process. While there are several residuals plots for testing the goodness of fit for the Cox model [2], the residuals plot for the additive models is limited. Arjas' plot was used to assess the adequacy of the fit of the additive model [17, 31-33]. The concept behind Arja's plot is to plot expected number of failures against actual number of the injury event with different covariate values. Arjas' plot is not a true residual plot, but deviations from the 45^o slope will give essentially the same information, which is a clearer indication of lack of model fit.

SAS version 9.2 and R were used for the analysis in this study. The additive hazards models are not available in commonly used computer packages, while for the Cox model most statistical software are readily available and easy to use to fit models, check model assumptions and assess model fit. Both the Aalen and L-Y additive hazards models can perform by either a SAS macro available at http://www.mcw.edu/FileLibrary/Groups/Biostatistics/Software/addmacro.txt [34] or a combination of PROC PHREG and PROC REG [33].

4. APPLICATION TO INJURY PREVENTION STUDY

A total of 1,467 subjects (789 from the intervention group and 678 from the control group) were eligible for the present study. Of these subjects, 263 subjects had the event of the TLR related injury with 114 (14.4%) from the intervention group and 149 (22%) from the control group. Our study ~~observation~~ duration was from January 1, 1999 to ~~completed at~~ December 1, 2006. The Kaplan-Meier analysis was performed to assess the overall difference among the intervention and control groups [35]. This result indicated that before 8 months the two survival curves were very close. After 8 months, the intervention

group had a higher probability of survival as compared to the control group (p=0.0013 for log-rank test and p=0.0063 for Wilcoxon test; Figure 1).

4.1. Cox's multiplicative model

The result of Cox model showed that group, occupation, and body parts were significant (Table 1). No significant interaction was observed between covariates. The intervention group had a 27% lower risk of injury as compared to the control group after controlling for occupation, and body parts (hazard ratio (HR)=0.63; 95% CI=[0.497, 0.804]; p=0.0002). Nurses and nursing aides (NNA) had a 72% higher risk of injury compared to Non-NNA (HR=1.72; 95% CI=[1.219, 2.416]; p=0.002). The back, neck and shoulder (BNS) were the most injured body parts. Compared to other body parts (Non-BNS), the back, neck and shoulder (BNS) had a 115% increased risk of injury (HR=2.15; 95% CI=[1.618, 2.85]; p<0.0001). Martingale residuals are used to check the overall fit of the multiplicative hazards model for the intervention and control groups (Figures 2). Martingale residuals showed that the fit of the multiplicative hazards model is questionable.

4.2. Aalen's additive model

In order to visualize a covariate effect over time, the estimated cumulative regression function has been examined, along with its upper and lower 95% point-wise confidence limits. The plot of the estimated cumulative regression functions for group showed that there was no covariate effect on the hazard up to 8 months. However, the slope was negative and clear effects of decreasing hazard for the period of 8-24 months but after that it was approximately constant hazard (Figure 3-a). Based on the estimated cumulative regression functions, it has been concluded that intervention group had the less risk of the injury event as compared to the control group. There may be time varying occupation effect because the cumulative regression function shows the non-zero slope over time (Figure 3-b). It has been observed that the effects of occupation have been increased in hazard up to 10 months, disappearing afterwards. For body parts, Figure 3-c also shows the positive slope over time and the 95% confidence limits of the covariate effects did not includes zero.

4.3. Lin and Ying's additive model

The result of L-Y additive hazards model showed that group, occupation and body parts were significant effect on the injury event (Table 2). The intervention group was significantly different for the injury event comparing to the control group (p-value=0.0005). The estimate is negative (-0.0025), indicating that the intervention group had protection from injury as compared to the control group. This is interpretable as the intervention group had 0.0025 less injuries than the control group after adjusting for occupation and body parts. It means that 25 person injuries can be prevented per 10,000 persons by the injury prevention program. Regarding occupation, nurses and nursing aides (NNA) had the significantly different on injuries than non-nurses occupations (Non-NNA). NNA had 0.0024 excess risk of injuries (excess risk (ER) =0.0024; p-value=0.0005; 95% C.I=[0.001, 0.0038]), which indicates that NNA had 24 more injury compared to non-NNA per 10,000. Similarly, the body parts, combined back, neck & shoulder had 0.0038 excess risk of injury than other body parts (ER=0.0038; p-value <0.0001; 95% CI=[0.0025, 0.0051]). The Arjas plots were used for the selected covariates to check the adequacy of the model. Figures 4-a shows that the plot are close to 45^{o}, indicating the group fits the model well. Notably, the Arjas plot of nurses and nursing aides is not long enough, but it reasonably satisfies the model (Figure 4-b). However, for the body parts, the plot is concave downwards and the deviations from the optimal fit was shown (Figure 4-c).

5. DISCUSSION

We showed the differences in estimates of the coefficients from the Cox multiplicative hazards model and the additive hazards models and their interpretation using an injury prevention program implemented for the healthcare workers. The Cox multiplicative and L-Y additive hazards models gave similar results with regard to covariates selected to be significant: group, occupations, and body parts. The estimates from the models also had the same signs, indicating the same directions of the covariate effects. Based on our analysis, both the Cox and L-Y models, as well as Aalen's additive hazards model, showed that the injury intervention program had a significant impact on reducing the

TLR related injures induced by patient handling among healthcare workers.

The parameter estimates and the standard errors from the Cox multiplicative and L-Y additive hazards models are noticeably different. While the coefficients of the Cox model act in a multiplicative way on unknown baseline hazards, those of the additive hazards models act in an additive way on unknown baseline hazards. Because the coefficients act in different ways in the multiplicative and additive hazards models, it is very difficult to compare them directly. Moreover, the Cox model gives a higher estimate than additive model when using a more compromised covariate profile probably due to the multiplicative effect of fixed covariate on baseline function [11]. The association between the covariates and the time to injuries in the additive hazards models was explained in terms of the risk difference or excess risk rather than the risk ratio. Thus the different models interpreted the coefficients in different ways.

The Cox model is most widely used; however, the proportional hazard assumption may not always be satisfied in the data. In such cases, there are various ~~solutions~~ alternatives to consider, for example, inclusion of a time-dependent covariate or stratification. In Aalen's model, and the main focus was the cumulative regression plots, where the slope of the plots at any given time provides information on the influence of the covariate at that moment. From a practical ~~stand~~point~~,~~ the graphical representation of the cumulative regression functions is attractive, because it provides a direct perception of data and a picture of how effects and the model fit in with change over time. Even one visualizes all covariate effects over time, and a simple interpretation of the effects is not possible, which makes Aalen's model less appealing in real applications than other models. However, it is still useful particularly when we are interested in temporal effects. The unknown risk coefficients used in Aalen's model are replaced by a constant covariate effect in the L-Y ~~model~~ additive hazards model. A theoretical limitation of the L-Y model is that the linear predictors in the model constrain to be positive [13]. Research on the additive hazard model in relation to generalizing estimating function to the case of multivariate failure time data as well as methods for checking the adequacy of the model is still rare. While various statistical software packages are available for fitting the Cox

model, the procedure is limited to some software for the additive hazards model. Few macros are available for the analysis of goodness of fit [17, 34].

Generally, the preference between the Cox hazards model and the additive hazards model is normally a practical matter. Although in theory, either model can provide adequate fit to a given time to event dataset, the more parsimonious one will unquestionably be preferable to clinical investigators. One of the major advantages of using the additive hazards model over the Cox multiplicative hazards model is that the resulting regression parameter estimator has a closed form. In cases where both the additive and multiplicative models fit the data fairly well, an additive specification may be preferred, due to the easy interpretation of the regression parameters. Regression coefficients from the additive model give more sensible and interpretable in public health research or patient management/care, where the risk difference can be more important than the risk ratio in understanding an association between a risk factor and disease occurrence [13, 17].

In summary, the Cox multiplicative and additive hazards models describe different features of the association between the risk factors and the study outcomes. These hazards models give different information and should not be viewed as alternative to each other. Rather it seems desirable to use together to gain a more comprehensive understanding of the data. Practitioners may benefit from these approaches, which help in predicting the effect of one or more variables and in verifying their influence on the study outcomes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Society: Series B. 1972;34:187–220.

2. Kalbfleisch JD and Prentice RL. ~~The s~~Statistical analysis of failure time data~~,~~ ~~Wiley,~~ New York: Wiley; 2002.

3. Aalen OO. Further results on the non-parametric linear regression model in survival analysis. Statistics in Medicine. 1993;12:1569–1588.

4. Andersen PK and~~,~~ Vaeth M. Simple Parametric and Nonparametric Models for Excess and Relative Mortality. Biometrics. 1989;45:523-35.

5. Mau J. On a Graphical Method for the Detection of Time-dependent Effects of Covariates in Survival Data. Applied Statistics-Journal of the Royal Statistical Society: ~~-~~Series C. 1986;35:245-55.

6. Mau J. A comparison of counting process models for complicated life histories. Applied Stochastic Models and Data Analysis. 1988;4:283-98.

7. McKeague IW. Estimation for a Semimartingale Regression Model Using the Method of Sieves. Annals of Statistics. 1986;14:579-89.

8. Huffer FW, McKeague IW. Survival analysis using additive risk models, T~~t~~echnical R~~r~~eport. Department of Statistics, Stanford University~~,~~;1987.

9. McKeague IW and~~,~~ Utikal KJ. Goodness-of-Fit Tests for Additive Hazards and Proportional Hazards Models. Scandinavian Journal of Statistics. 1991;18:177-95.

10. Bhattacharyya M and Klein JP. A note on testing in Aalen's additive hazards regression models. Statistics in Medicine. 2005;24:2235-40.

11. Lin DY and Ying ZL. Semiparametric Analysis of the Additive Risk Model. Biometrika. 1994;81:61-71.

12. Lin DY and Ying ZL. Semiparametric analysis of general additive-multiplicative hazard models for counting processes. The Annals of Statistics. 1995;23:1712-34.

13. Lin DY and Ying ZL. Additive regression models for survival data. Proceedings of the First Seattle Symposium in Biostatistics: Survival Analysis, Springer, New York. 1997;185–198.

14. Klein JP. Modelling competing risks in cancer studies. Statistics in Medicine. 2006;25:1015–1034.

15. Zhang X, Akcin H, and Lim HJ. Regression Analysis of Competing Risks Data via Semi-Parametric Additive Hazards Model. Statistical Methods and

Applications. 2011;20:357-381.

16. Yin G and Cai J. Additive hazards model with multivariate failure time data. Biometrika. 2004;91:801–818.

17. Lim HJ and Zhang X. Semi-parametric additive risk models: Application to injury duration study. Accident Analysis and Prevention. 2009:41:211-6.

~~18.~~ Lim HJ and Zhang X. Additive and multiplicative hazards modelling for recurrent event data analysis. BMC Medical Research Methodology. 2011;11:101 ~~doi: 10.1186/1471-2288-11-101.~~

18.

19. Martinussen T and Scheike TH. A flexible additive multiplicative hazard model. Biometrika. 2002;89:283-98.

20. Scheike TH and Zhang MJ. An additive-multiplicative Cox-Aalen model. Scandinavian Journal of Statistics. 2002;28:75–88.

21. Scheike TH and Zhang MJ. Extensions and applications of the Cox-Aalen survival model. Biometrics. 2003;59:1033–45.

22. Zahl PH. Regression analysis with multiplicative and time-varying additive regression coefficients with examples from breast and colon cancer. Statistics in Medicine. 2003;22:1113–27.

23. Cortese G and Scheike TH. Dynamic regression hazards models for relative survival. Statistics in Medicine. 2008;27:3563–84.

24. Cortese G, Scheike TH, and Martinussen T. Flexible survival regression modeling. Statistical Methods in Medical Research. 2010;19::5–28.

25. Lim HJ, Black TM, Shah SM, Sarker S, and Metcalfe J. Evaluating Repeated Patient Handling Injuries Following the Implementation of A Multi-factor Ergonomic Intervention Program among Health Care Workers. Journal of Safety Research. 2011;42: 185-191.

26. Black TM, Shah SM, Busch AJ, Metcalfe J, and Lim HJ. Effect of Transfer, Lifting and Repositioning (TLR) injury prevention program on musculoskeletal injury among direct care workers. Journal of Occupational & Environmental Hygiene. 2011;8:226-235.

27. Cox DR and Oakes D. Analysis of Survival Data~~,~~. London: Chapman & Hall~~;~~ 1984.

28. Aalen OO. A Linear-Regression Model for the Analysis of Life Times. Statistics in Medicine. 1989;8~~:~~907-25.

29. Klein JP and Moeschberger ML. Survival Analysis: Techniques for Censored and Truncated Data. New York: Springer;. 2003.

30. Aalen OO. Model for Nonparametric Regression Analysis of Counting Processes. Lecture Notes in Statistics. 1980;2:1-25.

31. Arjas E. A Graphical Method for Assessing Goodness of Fit in Cox Proportional Hazards Model. Journal of the American Statistical Association. 1988;83:204-12.

32. Torner A. Proportional Hazards and Additive Regression Analysis of Survival for Severe Breast Cancer. Technical Report. Stockholm: Stockholm University, Mathematical Statistics. 2004.

33. Schaubel DE and Wei G. Fitting the additive hazards model using standard statistical software. Biometrical Journal. 2007;49:719-730.

34. Howell AM. SAS Macro for the Additive Hazards Model. Master's Thesis,: Medical College of Wisconsin, BiostatisticsMilwaukee, USA, . 20071996.

35. Kaplan EL and Meier P. Nonparametric Estimation From Incomplete Observations. Journal of the American Statistical Association. 1958;53:457-81.

Table 1. Estimation of coefficient, hazard ratio, 95% confidence interval, and p-value from the Cox multiplicative hazards model.

Covariate	Estimate (S.E)	H.R	95% C.I	p-value
Group	-0.469 (0.128)	0.63	0.497, 0.804	0.0002
Occupation	0.540 (0.175)	1.72	1.219, 2.416	0.002
Body Parts	0.764 (0.144)	2.15-	1.618, 2.850	<0.0001

*S.E.: Standard Error; * HR: Hazard Ratio; * CI: Confidence Interval
Note: In this analysis, the reference group: Control group, , non-nurses for occupation (Non-NNA), and other body parts except back, neck and shoulder for body parts (Non-BNS)

Table 2. Estimation of coefficient, excess risk, 95% confidence interval, and p-value from the Lin and Ying's additive hazards model.

Covariate	Estimate (S.E)	E.R	95% C.I	p-value
Group	-0.0025 (0.0007)	-0.002	-0.0039, 0.0010	0.0005
Occupation	0.0024 (0.0006)	0.002	0.0010, 0.0038	0.0005
Body Parts	0.0038 (0.0006)	0.003	0.0025, 0.0051	<0.0001

S.E.: Standard Error; * ER: excess risk; * CI: Confidence Interval
Note: In this analysis, the reference group: Control group, , non-nurses for occupation (Non-NNA), and other body parts except back, neck and shoulder for body parts (Non-BNS)

Figure 1: Estimated survival probability curve by group.

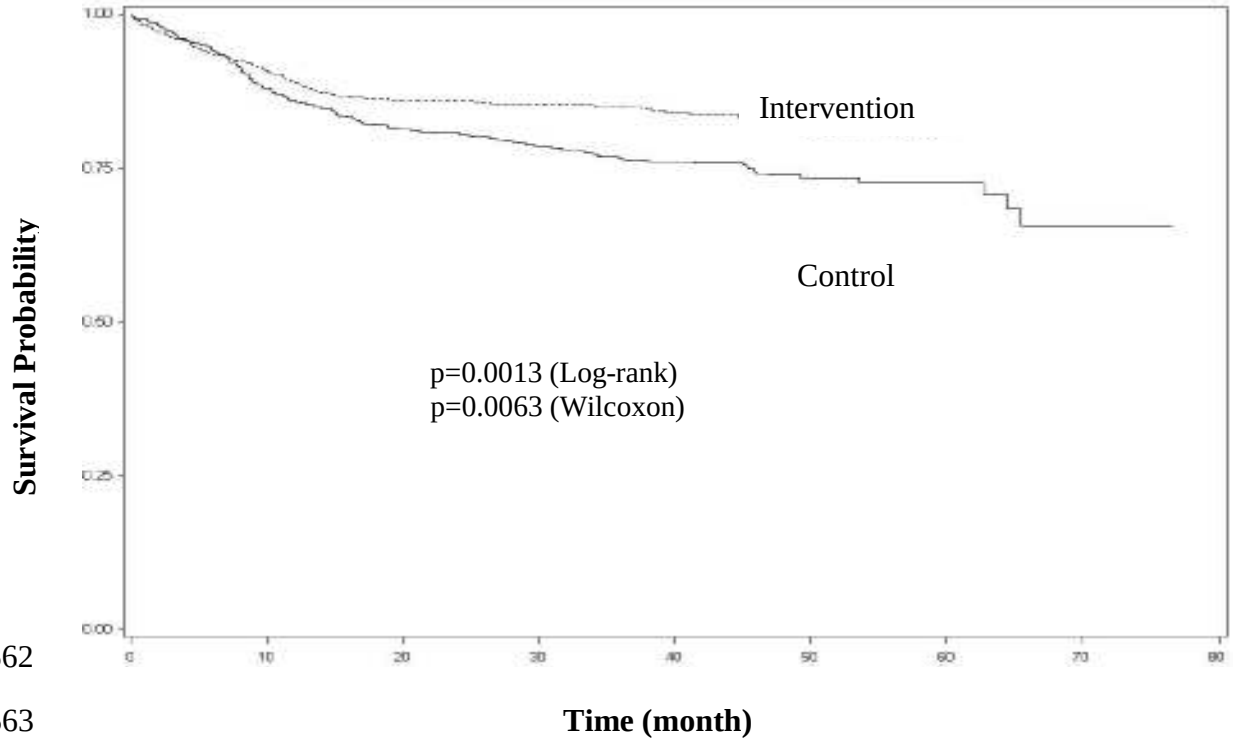


Figure 2: Martingale residuals plot for the multiplicative model.

Estimated Cumulative Hazards

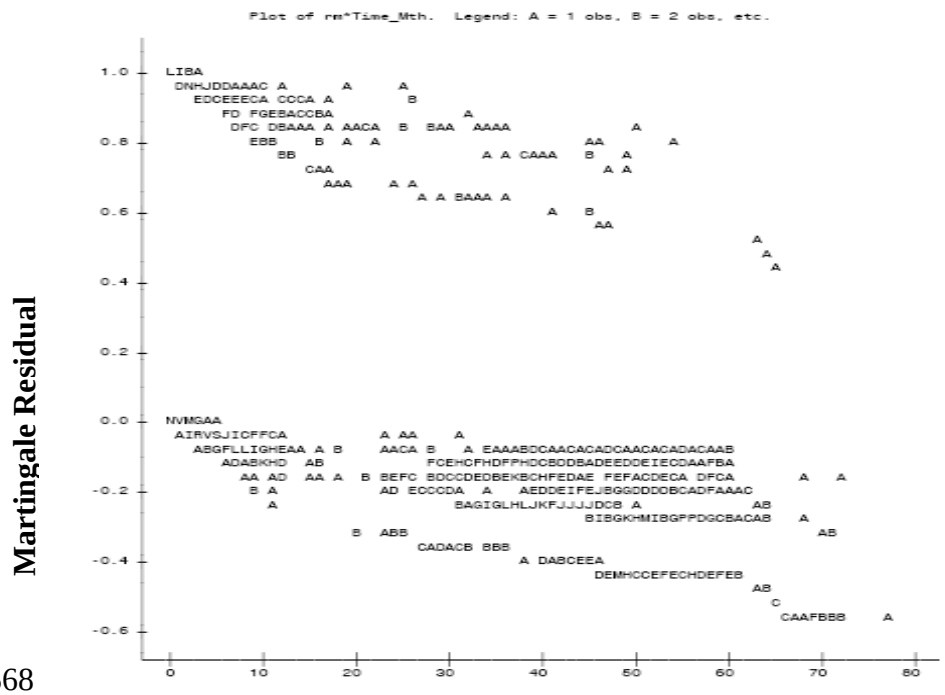


Figure 3-a: Estimated cumulative regression function by Aalen's additive model with its upper and lower 95% point-wise confidence limits for group.

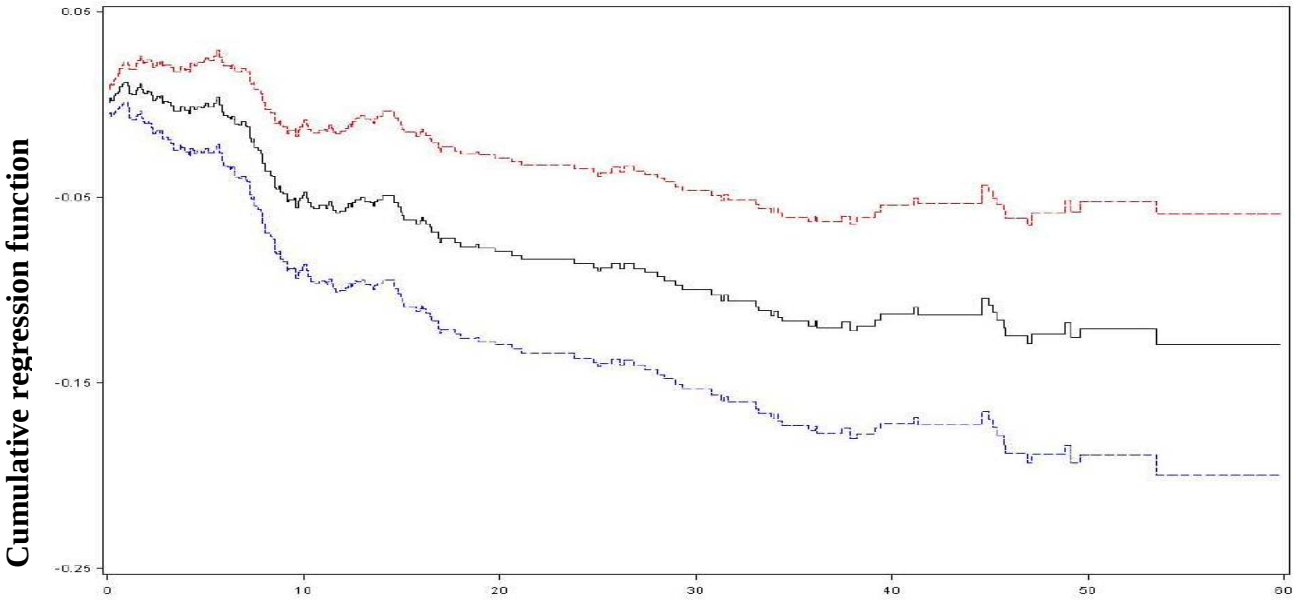


Figure 3-b: Estimated cumulative regression function by Aalen's additive model with its upper and lower 95% point-wise confidence limits for occupation.

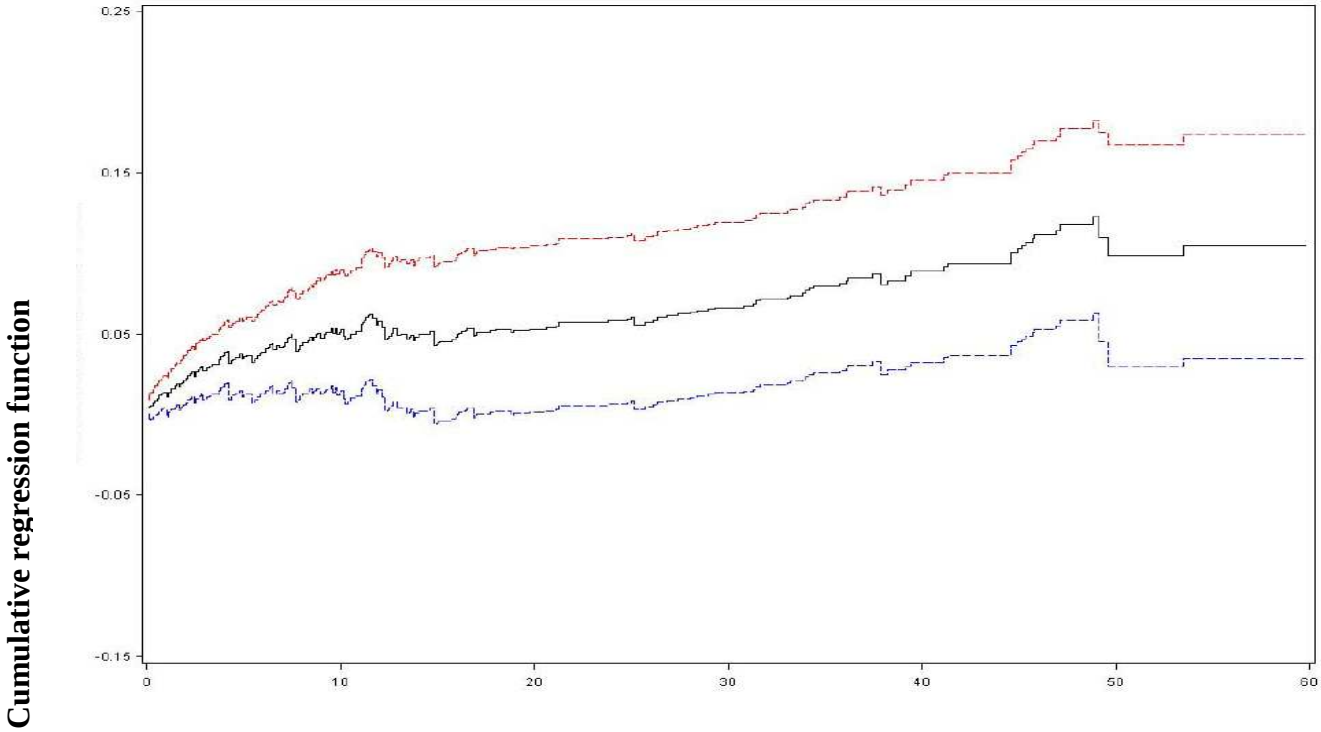


Figure 3-c: Estimated cumulative regression function by Aalen's additive model with its upper and lower 95% point-wise confidence limits for body parts.

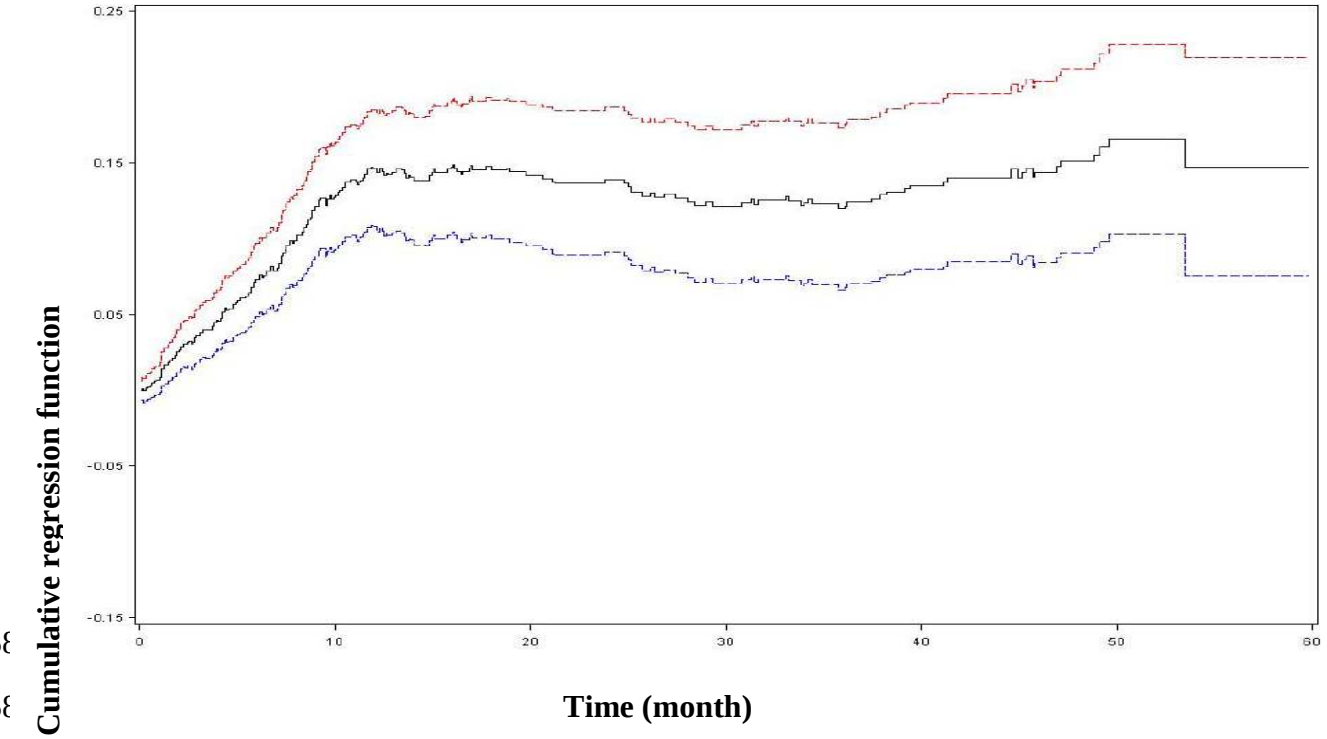


Figure 4-a: Arjas plot of the estimated cumulative hazard by group.

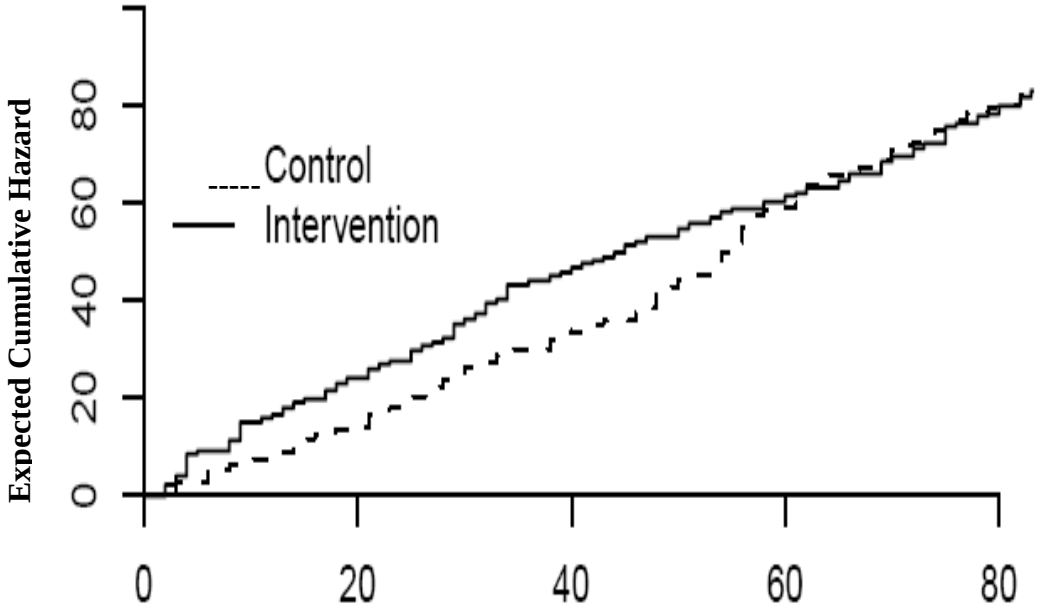
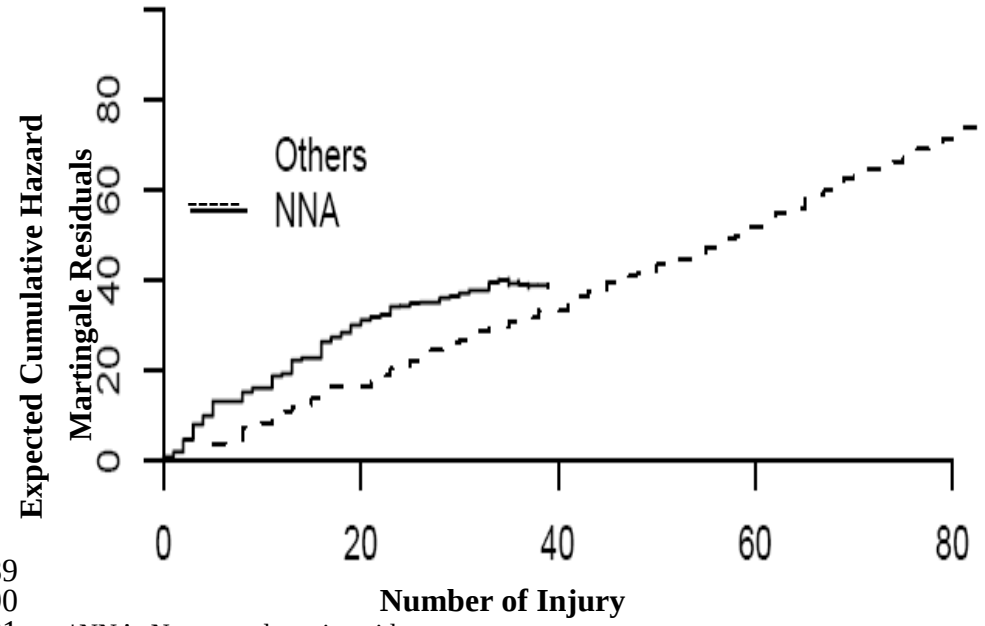


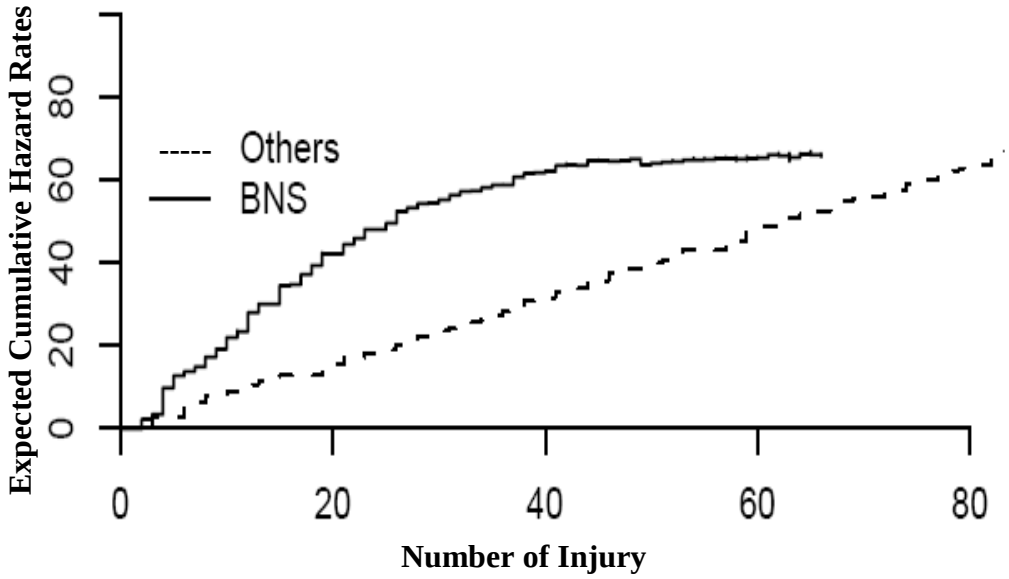
Figure 4-b: Arjas plot of the estimated cumulative hazard by occupation.



*NNA: Nurses and nursing aides

*Others include therapists, technicians, unit supporters, paramedics, etc.

Figure 4-c: Arjas plot of the estimated cumulative hazard for the additive model by body parts.



* BNS: Back, neck and shoulder

* All other body parts include abdomen, chest, face, etc.