A linearity test for the factors affecting survival of Immunosuppressive Treatment (IST) and International Myelodysplasia Risk Analysis Workshop (IMRAW) patients using restricted cubic splines.

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1. Introduction

"A myelodysplastic syndrome (MDS) is a type of cancer in which the bone marrow does not make enough healthy blood cells and there are abnormal cells in the blood or bone marrow."[1]

"Death from MDS is due to progression to acute leukemia or to the consequences of cytopenias."[2]

There are 816 patients with Myelodysplastic Syndrome (MDS) response to International Myelodysplasia Risk Analysis Workshop (IMRAW) who received a comparable supportive care, compared with patients who received Immunosuppressive Treatment (IST) at National Institute of Health (NIH) in order to determine their clinical course.[3]

This primary objective of this project is to test the linearity for those covariates which affecting survival time of Immunosuppressive Treatment (IST) patients and International Myelodysplasia Risk Analysis Workshop (IMRAW) patients by using restricted cubic splines. Moreover, this project is based on the paper "Factors Affecting Response and Survival in Patients With Myelodysplasia Treated With Immunosuppressive Therapy" by Elaine M. Sloand, Colin O. Wu, Peter Greenberg, Neal Young, and John Barrett.

2. Method

Definition[4]
The restricted spline function with k knots $t_1,t_2,...,t_k$ is given by,

$$f(X) = \beta_0 + \beta_1 X + \beta_2 X_1 + \cdots + \beta_k X_{k-1},$$

(1)

Where $X_1 = X$ and for $j = 1, \ldots, k-2$,

$$X_j = (X - t_j)^3 - (X - t_{j+1})^3 (t_j - t_{j+1}) (t_j - t_j) + (X - t_{j+1})^3 (t_{j+1} - t_{j+1}) (t_j - t_{j+1})$$

(2)

Theorem[5]
Once $\beta_0, \ldots, \beta_k$ are estimated, the restricted cubic spline can be restated in the form,

$$f(X) = \beta_0 + \beta_1 X + \beta_2 (X - t_1)^3 + \cdots + \beta_k (X - t_k)^3,$$

(3)

By computing,

$$\beta_i = (\beta_i (t_i - t_i) + \beta_i (t_i - t_i) + \beta_i (t_i - t_i)) (t_i - t_i),$$

(4)

$$\beta_{i+1} = (\beta_{i+1} (t_{i+1} - t_{i+1}) + \beta_{i+1} (t_{i+1} - t_{i+1}) + \beta_{i+1} (t_{i+1} - t_{i+1})) (t_{i+1} - t_{i+1}),$$

(5)

Moreover, applying the predict function on the outcome, a less skewed. Then apply on the covariates which have significant p values in the nonlinearity test in Table 2. Moreover, applying the predict function on the outcome, a table of correlation with time after transformation and NIH of all the covariates.

Table 3. Correlation with time after transformation and Table 4. Linear test after transformation with NIH as stratification

4. Discussion

Fitting all the variables into cox proportional hazard model with applying restricted cubic splines method, the result shows in Table 1. The covariate PLATE, BLASTS and NEUTRO are highly skewed as shown in Figure 2, so use log and square root function to transform them and make them less skewed. Then apply on the covariates which have significant p values in the nonlinearity test in Table 2. Moreover, applying the predict function on the outcome, a table of correlation with time after transformation can be produced. Only NIH and log(NEUTRO+1)are significant with time effect. Hence, considering NIH as a stratification. Do the linearity test again to the new model with NIH as a stratification, we have table 4 which shows the linearity of all the covariates.

5. Reference

[1] National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/myelodysplastic
[2][3] Elaine M. Sloand, Colin O. Wu, Peter Greenberg, Neal Young, and John Barrett, "Factors Affecting Response and Survival in Patients With Myelodysplasia Treated With Immunosuppressive Therapy".


Figure 1. Tables of summary for continuous variables and categorical variables

Figure 2. Skew test of covariate PLATE, BLASTS and NEUTRO

Figure 3. Spline-smoothed scaled schoenfeld residuals for log(NEUTRO+1) and NIH

Table 1. Linearity test and Table 2. Linearity test after transformation