PhUSE 2013

Paper SP07

Extensions of Cox Model for Non-Proportional Hazards Purpose

Jadwiga Borucka, PAREXEL, Warsaw, Poland

ABSTRACT

Cox proportional hazard model is one of the most common methods used in analysis of time to event data. The idea of the model is to define hazard level as a dependent variable which is being explained by the time-related component (so called baseline hazard) and covariates-related component. Model is based on several restrictive assumptions which need to be carefully verified before interpretation of parameters estimates. One of them is the assumption of proportional hazard which results directly from the model formula and means that hazard ratio needs to be constant over time. However, if this assumption is violated, it does not necessarily prevent analyst from using Cox model. The current paper presents two ways of model modification in case of non-proportional hazards: introducing interactions of selected covariates with function of time and stratification model. Both of them are easily applicable with the use of PHREG procedure in SAS®. The paper consists of introduction, two sections dedicated to the methods of non-proportional hazards handling and conclusions. References, acknowledgements and contact information are included at the end of this article.

INTRODUCTION

Cox proportional hazard model is one of the most common methods used in analysis of time to event data. The idea of the model is to define hazard level as a dependent variable which is being explained by the time-related component (so called baseline hazard) and covariates-related component. The model is defined as follows:

$$\lambda(t, \boldsymbol{x}) = \lambda_0(t) \exp(\beta \boldsymbol{x})$$

where:

$\lambda(t, \boldsymbol{x})$ – hazard function that depends on timepoint t and vector of covariates **x**,
$\lambda_0(t)$ – baseline hazard function that depends on time only,
$\exp(\beta \boldsymbol{x})$ – covariates-related component.

Cox model is based on several restrictive assumptions. One of them is the assumption of proportional hazard that the name of the model refers to and which results directly from the model formula as follows:

$$HR = \frac{\lambda(t, \boldsymbol{x}_1)}{\lambda(t, \boldsymbol{x}_2)} = \frac{\lambda_0(t)\exp(\beta \boldsymbol{x}_1)}{\lambda_0(t)\exp(\beta \boldsymbol{x}_2)} = \frac{\exp(\beta \boldsymbol{x}_1)}{\exp(\beta \boldsymbol{x}_2)} = \exp\left[\beta(\boldsymbol{x}_1 - \boldsymbol{x}_2)\right]$$

where:

HR – hazard ratio,
$\mathbf{x}_1$ – vector of covariates of subject I,
$\mathbf{x}_2$ – vector of covariates of subject II.

The assumption states that hazard ratio for two subjects who are characterized by different sets of covariates depends only on values of these covariates and does not depend on time. In other words: hazard ratio is constant over time which means that the effect of the given covariate on the hazard level is the same at all timepoints. There are various opinions on the importance of this assumption with regard to the parameters interpretation. Some authors state that violation from it is nothing extremely problematic as in such cases parameter for a covariate for which assumption is not satisfied can be understood as 'average effect' over timepoints that are observed in a dataset (Allison, 1995). The others however underline the importance of this assumption (Hosmer, Lemeshow 1999) and suggest potential modification of the model if hazard ratio turns out not to be constant over time for some covariates. While in some situations measuring 'average effect' of a covariate for which proportional hazard assumption is not satisfied might be enough, it is possible to recall cases where this approach is not satisfying. Hosmer and Lemeshow (1999) discuss this issue and give an example of randomized clinical trials in which site is

relatively often being used as a covariate in Cox model. Such an approach results in assuming that baseline hazards are proportional across study sites which might not necessarily be justified. In such cases it would be worth taking this fact into account and estimate the model adjusting for potentially time-varying effect of study site rather than stating that parameter estimate for site expresses its 'average effect' on the hazard level.

There are several methods that enable verification of proportional hazard assumption. Firstly, one can consider graphical method which is based on the plot of 'log-negative-log' of the Kaplan-Meier estimator of survival function presented separately for each group defined on the basis of values of a covariate for which the assumption is being verified (Hosmer, Lemeshow 1999). If the assumption is satisfied, plot should present several curves with distance between them that does not change over time. One possible disadvantage of this method might be the fact that it is quite problematic to visually assess how far these lines are from parallel position, especially for small samples. The other graphical method employs Schoenfeld residuals which are expected to have mean equal to 0 which might be assessed on the basis of the plot (it is expected that residuals will show no trend over time). The third method adds to the model interaction of the covariate of interest with time – if such a variable turns out to be statistically significant, it indicates that proportional hazard assumption might be violated. The last method is not only a way to verify the assumption but also a potential solution to the problem of its violation, which will be discussed wider in the next section.

As soon as it is stated that proportional hazard assumption is not satisfied for a covariate, it should be decided which approach is to be chosen. As it was mentioned before, one can think of the parameter estimate as of the average strength of the covariate impact on the hazard rate. If this is the case, nothing more should be done in terms of Cox model construction. If the influence however varies over time and this changing impact is also of interest, then one of the available methods of Cox model modification for non-proportional hazards might be applied. There are two methods that are being considered most often: adding covariate to the model which is defined as an interaction of particular covariate with a function of time variable and stratification model. The next two sections present these methods, including example application on the dataset containing data for 60 subjects from open-label clinical trial: age at screening (in years), site (coded as SITE = 1 that corresponds to site B or SITE = 2 that corresponds to site A) and time since the beginning of study to death/censoring (in days) as well as censoring information (coded as CENSOR = 1 for subjects who experience the event, here: death, and CENSOR = 0 otherwise). Cox model is used in order to analyze time to death among subjects enrolled in the study, with regard to age of patients and study site. For presenting purpose, simple Cox model is being considered, including age and site as explanatory variables. All calculations are being performed with the use of statistical and graphical procedures in SAS Base 9.3.

INTERACTION WITH TIME

The first method uses interactions with time for covariates for which assumption is not satisfied. This method is in fact both the way to identify such covariates in the model and solution of the problem at the same time (Allison, 1995). After adding an interaction of some function of time variable with a covariate included in the initial model, the statistical significance is being verified. If newly added variable turns out to be significant, it indicates that proportional hazard assumption is not satisfied for the given covariate which means that its effect is changing over time. Including the interaction in the model enables interpretation of the parameters that takes into consideration the fact that the covariate's influence on the hazard level is not constant. As far as the function type is concerned, some authors suggest using logarithm rather than any other function (Quantin, et al., 1996), the others however underline that there is no theoretical reason to choose logarithm as this approach is seen rather as a technical solution that enables to avoid numerical problems (Allison, 1995). PHREG procedure is said to be robust to such problems (Allison, 1995), thus simple linear function is chosen.

The sample dataset is being used to estimate the Cox proportional model, where the event is defined as death of patient, time is measured from the beginning of the open-label study, age and site are included as covariates. The exact method according to Kalbfleisch and Prentice (1980) is being used in model estimation in order to account for presence of tied evens in the dataset. The following piece of code estimates the model, using TIME as time variable, CENSOR as censoring indicator (0 means lack of event), AGE and SITE as covariates.

```
/*Initial Cox model estimation – site and age as covariates*/
proc phreg data = a.site;
       format site site.;
       model time*censor(0) =  age site  / ties = exact;
       output out = schoen ressch = age_s site_s ;
run;
```

Model 1:

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.20690	0.07405	7.8069	0.0052	1.230
SITE	1	-0.74290	0.38926	3.6423	0.0563	0.476

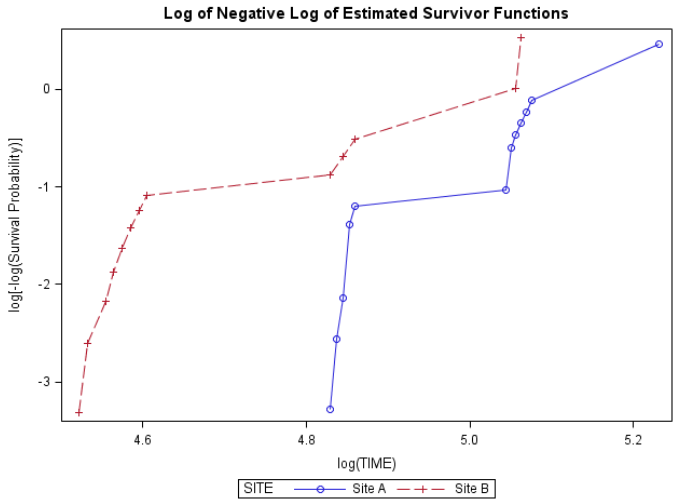
Convergence criterion is satisfied, both covariates are significant at the level of 0.1.
The proportional hazard assumption is being verified for both variables, using interactions with time and Schoenfeld residuals plots. For categorical variable SITE, additionally plot of 'log-negative-log' is presented.

Proportional hazard assumption verification for SITE:

(1) Plot of 'log-negative-log' of survival function:

'Log-negative-log' of survival function plots are being obtained with the use of LIFETEST procedure with STRATA statement, as follows:

```
/*Lifetables estimation according to Kaplan-Meier formula;
generation of the plot of 'log-negative-log' of survival function
separately for each site -> STRATA statement*/
proc lifetest data = a.site plots = (s, lls);
       format site site.;
       strata site;
       time time*censor(0);
run;
```

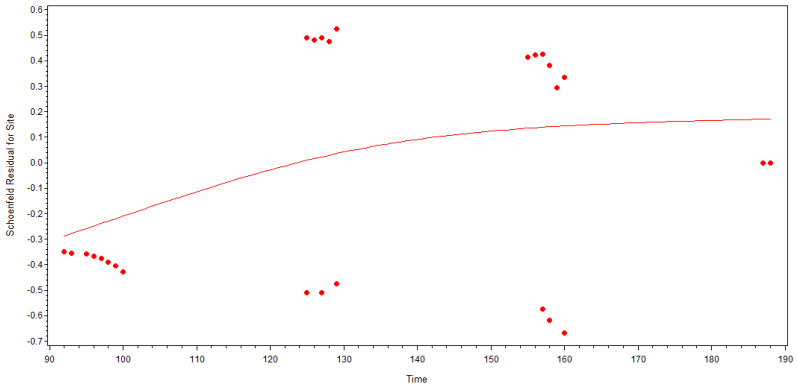


(2) Plot of Schoenfeld residuals:

In order to obtain Schoenfeld residuals plots, it is necessary to estimate Cox model using PROC PHREG and save Schoenfeld residuals in a separate dataset, adding OUTPUT OUT statement. Then, GPLOT procedure enables to generate the plot of residuals as a function of time.

```
/*Cox model estimation - age and site as covariates;
saving Schoenfeld residuals in output dataset*/
proc phreg data = a.site;
       format site site.;
       model time*censor(0) =  age site  / ties = exact;
       output out = schoen ressch = age_s site_s ;
run;
```

```
/*Generation of plot of Schoenfeld residuals for site as function of time*/
proc gplot data = schoen;
       symbol1 v = dot c = red width = 1 i = sm80s;
       plot site_s*time / haxis = axis1 vaxis = axis2;
       axis1 label = ('Time');
       axis2 label = (a = 90 'Schoenfeld Residual for Site');
run;
```



(3) Interaction of SITE with TIME variable:

Adding interaction with time to the Cox model is quite simple in PHREG procedure. The additional variable needs to be named in the MODEL statement and then defined, using programming statements available in the procedure.

```
/*Cox model estimation - age and site as covariates, with interaction of site
and time added*/
proc phreg data = a.site;
       format site site.;
       model time*censor(0) = age site site_t/ ties = exact;
       site_t = site*time;
       test: test site_t;
run;
```

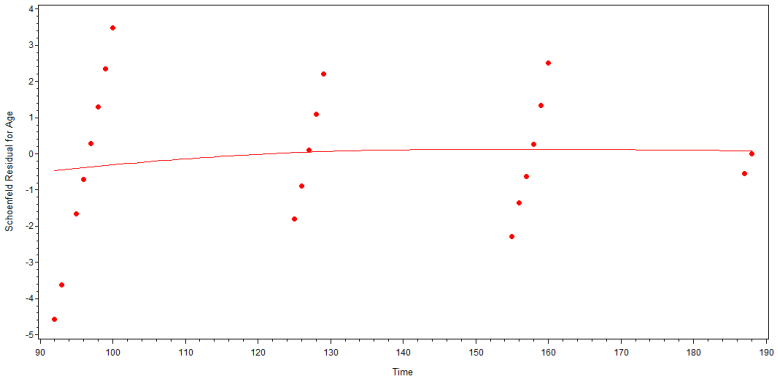
Model 2:

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.23313	0.07399	9.9268	0.0016	1.263
SITE	1	-5.90164	2.80362	4.4311	0.0353	0.003
site_t	1	0.03985	0.02123	3.5233	**0.0605**	1.041

Proportional hazard assumption verification for AGE:

(1) Plot of Schoenfeld residuals:



(2) Interaction of AGE with TIME variable:

Model 3:

Analysis of Maximum Likelihood Estimates

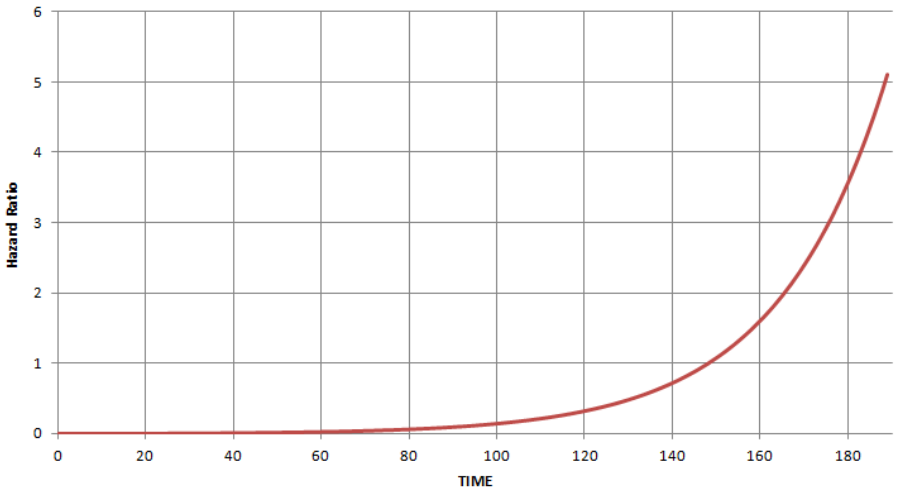
Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.01692	0.38357	0.0019	0.9648	1.017
SITE	1	-0.70788	0.39323	3.2406	0.0718	0.493
age_t	1	0.00149	0.00296	0.2516	0.6160	1.001

On the basis of the above results it can be stated that proportional hazard assumption seems to be satisfied for AGE – interaction of AGE and TIME is not statistically significant at any acceptable level, Schoenfeld residuals on the plot do not show any trend, smoothed line has approximate zero slope. For SITE however, conclusion seems to be quite opposite – interaction with time is statistically significant at the level 0.1. Plot of Schoenfeld residuals does not give straightforward answer however it might suggest that hazards are not proportional across study sites which can be stated also on the basis of 'log-negative-log', as distance between lines is not constant for all values of TIME. This might lead to the conclusion that proportional hazard assumption is violated for SITE variable and effect of this variable might be changing over time. Thus, it would be worth considering the model including interaction of SITE and TIME. Comparing Model 1 (initial one) and Model 2 (with TIME by SITE interaction added) it can be seen that information criteria have lower values in Model 2. Likelihood ratio test in this case is in fact test for significance of TIME by SITE interaction, as it is the only covariate added, and leads to rejection of the null hypothesis which assumes that added variable is not significant. It seems then that adding new variable to the model resolves problem with violated assumption and improves fit statistics. Thus, considering two models presented above, Model 2 should be chosen rather than Model 1. Let's focus on the parameters interpretation for SITE variable in both models. As far as Model 1 is concerned, interpretation is quite straightforward. Parameter estimate equal to -0.7429 results in hazard ratio for binary variable at the level of 0.48 which means that subjects from site A are approximately 52% less likely to die than subjects from site B. Due to the fact that proportional hazard assumption is violated for SITE, this interpretation might only refer to 'average' effect of SITE, as suggested by Allison. Now, let's take into account the fact that effect of this covariate is changing over time. In order to calculate hazard ratio between site A and site B on the basis of Model 2 estimation, the following equation is being derived:

$$HR = \frac{\lambda(t, age = a, site = 2)}{\lambda(t, age = a, site = 1)} = \frac{\lambda_0(t)\exp\left[\beta_1 a + 2\beta_2 + 2\beta_3 \mathrm{t}\right]}{\lambda_0(t)\exp\left[\beta_1 a + \beta_2 + \beta_3 \mathrm{t}\right]} = \exp[\beta_2 + \beta_3 \mathrm{t}].$$

where:
β_1 – parameter estimate for age,
β_2 – parameter estimate for site,
β_3 – parameter estimate for interaction of site and time.

As it can be seen, hazard ratio depends on time thus interpretation of site effect on the hazard level should incorporate value of time variable as well. The plot below presents how hazard ratio between two subjects of the same age but from different sites changes over time.



On the basis of the plot it can be stated that hazard ratio is very low up to 80th day which means that for relatively low survival times subjects from site B are much more likely to die than subjects from site A, however hazard ratio constantly increases so this difference is becoming smaller and smaller. On 130th day subjects from site A are approximately 50% less likely to die than subjects from site B. Hazard ratio reaches value of 1 on 148th day which means that chances of dying are equal for subjects treated in both sites. After that time hazard ratio rapidly increases and exceeds 3 after 176th day meaning that eventually subjects from site A are even three times more likely to die than subjects treated in site B. It should be mentioned that the first event in the whole sample was recorded on 92nd day thus drawing conclusions for period 0 – 92 days might not be reliable and the interpretation should be focused rather on values of TIME greater than or equal to 92. In general, it might be stated that subjects from site B seem to experience the event relatively early but if they survive long enough, they are not likely to die in later phase. Subjects from site A are more likely to live longer but after some time point they seem to experience the event approximately as often as subjects from site B. To be more specific, 14 subjects from site B are dying between 92nd and 160th day, 17 subjects who die in site A have survival times between 125th and 188th day in the study. As compared with the results of Model 1, where it is stated that subjects from Site A are 'in average' approximately 52% less likely to experience the event, it is worth being mentioned that after accounting for the fact that effect of SITE is not constant over time, this difference turns out to be much higher at some time points and – what is more important – hazard ratio is lower than 1 in early phase (meaning that subjects from site B are more risky group) but exceeds 1 after 148th day indicating that subjects from site A become more likely to die.

STRATIFIED MODEL

The second method that enables to handle non-proportional hazards is stratification. The main idea is to split the whole sample into subgroups on the basis of categorical variable which is called stratification variable and re-estimate the model, letting the baseline hazard function differ between these subgroups. It makes sense to choose a categorical covariate as a stratification variable if it interacts with time (i.e. proportional hazard assumption is not satisfied for this covariate) and is not of primary interest as stratification of the model automatically excludes stratification variable from explanatory variables set. As far as coefficient estimates are concerned, in the basic form of stratified model it is assumed that they are constant across strata groups however it is possible to include interaction of a stratification variable and another covariate in order to take into account different slopes (Hosmer, Lemeshow 1999). In general, the stratified model for stratum s is defined as follows:

$$\lambda_s(t, \boldsymbol{x}) = \lambda_{s0}(t) \exp(\beta \boldsymbol{x})$$

where s = 1, 2, …, S and S is the total number of subgroups created on the basis of stratification variable. The partial likelihood function formula is similar to the function proposed by Cox having additional subscript indicating the stratum number. By multiplying partial likelihood function for each stratum, the full partial likelihood function is obtained (for details, please refer to Hosmer, Lemeshow 1999). After the stratified model is estimated, it is possible to obtain estimation of baseline survival and baseline cumulative hazard functions for each stratum. Additionally, one can estimate covariates-adjusted survival and cumulative hazard functions. There is available option BASELINE in PHREG procedure which enables to calculate obtain these estimates for each stratum. Calculations are being performed for each set of covariates that are specified by the user. If no input dataset containing specified sets of covariates is defined, then SAS calculates survival and cumulative hazard function for each value of stratification variable, taking the mean of continuous variables within each stratum.

Let's consider SITE for which it is known that proportional hazard assumption is violated as a stratification variable. It will be not possible to obtain parameter estimates for SITE, however using BASELINE statement enables to estimate survival and cumulative hazard function estimates for each site separately, adjusting for age. The Cox model is re-estimated in the modified formula, using STRATA statement in PHREG procedure.

```
/*Cox model estimation - AGE as a covariate, SITE as stratification variable;
saving estimates of survival and cumulative hazard functions in BASE dataset*/
proc phreg data = a.site;
      baseline out = base  survival = surv cumhaz = cumhaz;
      format site site.;
      strata site;
      model time*censor(0) = age / ties = exact;
run;
```

Model 4:

Summary of the Number of Event and Censored Values

Stratum	SITE	Total	Event	Censored	Percent Censored
1	Site A	30	17	13	43.33
2	Site B	30	14	16	53.33
Total		60	31	29	48.33

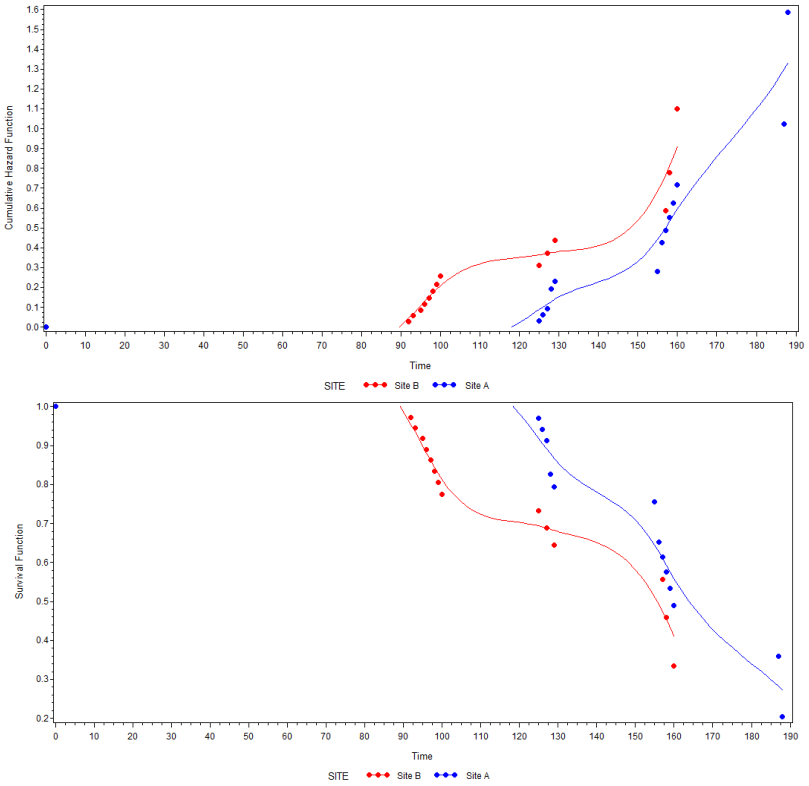
Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.20959	0.07534	7.7389	0.0054	1.233

Results of the model estimation are presented above. Convergence criterion is satisfied, AGE – which is the only covariate in the stratified model – is significant at any acceptable level. As it can be noticed, hazard ratio for AGE does not differ to a large extent as compared with Model 1 and is equal to 1.23, which means that every year the risk of dying increases by 23% as compared with the previous year. However, it should be taken into account that hazard ratio calculated by SAS concerns comparison of subjects with one year age difference. While comparing subjects with larger age difference, e.g. 20 years, hazard ratios are equal to 66 for stratified model and to 63 for initial model which makes the difference between the initial model and the stratified model more visible. Additionally, plots of cumulative hazard and survival functions are presented below.

```
/*Plots of covariates-adjusted cumulative hazard and survival functions
obtained on the basis of the stratified model*/
proc gplot data = base;
       symbol1 v = dot c = red width = 1 i = sm50s;
       symbol2 v = dot c = blue width = 1 i = sm50s;
       plot cumhaz*time = site / haxis = axis1 vaxis = axis2;
       axis1 label = ('Time');
       axis2 label = (a = 90 'Cumulative Hazard Function');

run;
```



As it is expected on the basis of previous results, subjects from site A tend to have relatively longer survival times as compared with subjects from site B. Cumulative hazard function for almost all time points is higher for site B which means that expected number of events till the given time point is usually higher for subjects treated in this site.

On the basis of the models presented above it can be stated that accounting for the non-proportional hazards (if exist) provides more detailed interpretation. Not only is it possible to state which group is more likely to experience the event but it is also possible to analyze hazard ratio that is changing over time and corresponds to varying effect of the given covariate. At the same time, it is hard to define a general rule saying which of the two methods presented above should be chosen. On the one hand, stratification model is easier to implement and requires less computational resources (Allison, 1995). On the other hand, if analysis is performed with the use of relatively small dataset or with the use of powerful computer, resources are not that important and interaction with time might be introduced to the model. The latter approach enables to obtain parameter estimate for covariate for which proportional hazard assumption is violated, as well as analyze how hazard ratio changes over time, which is impossible if stratification model is chosen. While trying to compare two models accounting for non-proportional hazards presented above, i.e. Model 2 including interaction of SITE by TIME and Model 4 based on stratification, information criteria and partial likelihood function values might be compared. Statistics corresponding to each model are presented in the table below. Additionally, fit statistics for initial model including SITE and AGE as covariates are included.

	SITE by TIME interaction	SITE as stratification variable	Initial model
-2lnL	163.593	142.361	168.051
AIC	169.593	144.361	172.051
SBC	173.895	145.795	174.919

It can be noticed that initial model (Model 1 including SITE and AGE as covariates) that neglects the fact that proportional hazard assumption is violated for SITE variable has the highest values of all three fit statistics. While comparing Model 2 and Model 4, it can be stated that all criteria have lower values for stratification model, which stands for this approach. Likelihood ratio test however cannot be performed in this case as considered models are not nested. Additionally – in order to perform an overall assessment of both models – linear predictor is being calculated and ten binary variables are created on the basis of its percentiles. Nine out of ten binary variables were introduced to the models and their statistical significance is being verified. The piece of SAS code presented below is being used to perform these procedures.

```
/*Overall assessment -  model with site by time interaction*/
data over1;
       set a.site;
       xbeta =  0.23313*age - 5.90164*site + 0.03985*site*time;
       count = 1;
run;

proc univariate data = over1 noprint;
       var xbeta;
       output out = perc pctlpre = p pctlpts = 10 20 30 40 50 60 70 80 90 100;
run;

data perc;
       set perc;
       count = 1;
run;

data over1a;
       merge over1 perc;
       by count;
run;

%macro ret;

data over1a;
 set over1a;

 if xbeta<=p10 then x10 = 1;
 else x10 = 0;
 if xbeta<p90 then x100 = 1;
```

```
 else x100 = 0;


%do i = 10 %to 80 %by 10;
%do j = 20 %to 90 %by 10;
      if xbeta>p&i and xbeta<=p&j then x&j = 1;
      else x&j = 0;
      %end;
      %end;
run;

%mend;

%ret;

proc phreg data = over1a;
model time*censor(0) = age site site_t x10 x20 x30 x40 x50 x60 x70 x80 x90 /
ties = exact;
      site_t = site*time;
run;
```

Model 2 (including SITE by TIME Interaction):

The PHREG Procedure

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.37049	0.10046	13.6010	0.0002	1.448
SITE	1	-6.95164	3.09349	5.0498	0.0246	0.001
site_t	1	0.04683	0.02330	4.0395	0.0444	1.048
x10	1	4.12871	1.40198	8.6726	**0.0032**	62.098
x20	0	0	.	.	.	.
x30	0	0	.	.	.	.
x40	0	0	.	.	.	.
x50	0	0	.	.	.	.
x60	0	0	.	.	.	.
x70	0	0	.	.	.	.
x80	0	0	.	.	.	.
x90	1	-1.55707	0.67801	5.2741	**0.0216**	0.211

Model 4 (SITE as stratification variable):

Analysis of Maximum Likelihood Estimates

Parameter	DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio
AGE	1	0.13433	0.09317	2.0788	0.1494	1.144
x10	1	-15.57684	1676	0.0001	**0.9926**	0.000
x20	0	0	.	.	.	.
x30	0	0	.	.	.	.
x40	0	0	.	.	.	.
x50	0	0	.	.	.	.
x60	0	0	.	.	.	.
x70	0	0	.	.	.	.
x80	0	0	.	.	.	.
x90	1	0.25073	0.59950	0.1749	**0.6758**	1.285

In stratification model, none of newly added variables is statistically significant at any acceptable level. As it comes to model with TIME by SITE interaction, two variables for which parameters estimates were obtained are significant which suggests poor fit of the model. Thus, comparison of information criteria as well as linear predictor method would suggest using stratification model rather than introducing interaction with time to the model. It should be noticed however that these tests should not be treated as an oracle as they give rather kind of suggestions rather than unequivocal determinant of decision which model should be chosen.

CONCLUSIONS

Although proportional hazard assumption is one of the most important features in Cox model, its violation should not definitely prevent from using this statistical tool. The current paper presents two methods that were developed in order to take into account the effect of a covariate that varies through time. Calculations performed give the evidence that stratification or including interaction with time results in better model fit in case of covariates for which proportional hazard assumption is not satisfied. Additionally, more detailed results and interpretation are obtained with the use of presented method. It would be hard however to define general rule for non-proportional hazards handling. The analyst can consider one of three possibilities, i.e. keeping all covariates in the model and neglecting the fact of the violation from non-proportional hazard assumption, introducing interaction of TIME by SITE and estimation of stratification model. Each of these approaches has its pros and cons. What is more, it is hard to compare these models, especially stratification model with non-stratified models, as they differ in their construction. Thus, as soon as non-proportional hazards are identified in the model, this fact should definitely be taken into consideration but the choice of the method needs to be adjusted for the particular example.

REFERENCES

Allison P. D., *Survival analysis using SAS. A practical guide*, 1995, Cary.
Hosmer D., Lemeshow S., 1999, *Applied survival analysis. Regression modeling time to event data,* New York.
Kalbfleisch J. D., Prentice R. L., 1980, *The statistical analysis of failure time data*, New York.
Quantin C, Moreau, T., Asselain B., Maccario J., Lellouch, J., 1996, *A regression survival model for testing the proportional hazards hypothesis*., in: Biometrics, 52.
Therneau T. M., Grambsch P. M., 2000, *Modeling survival data*, Berlin.

ACKNOWLEDGEMENTS

Special thanks to Marzena Marcinowska and Kirill Skouibine for their help and support.

CONTACT INFORMATION

Jadwiga Borucka, PAREXEL International
Marconich str. 6, 02-954 Warsaw, Poland
Tel. +48 22 452 1288
E-mail: jadwiga.borucka@parexel.com, jadwiga.borucka@gmail.com