PharmaSUG 2016 – Paper SP01

Cox proportional hazards regression to model the risk of outcomes per double increase in a continuous explanatory variable

Seungyoung Hwang, Johns Hopkins University, Baltimore, MD

ABSTRACT

The Cox proportional hazards model to explore the effect of an explanatory variable on survival is by far the most popular and powerful statistical technique. It is used throughout a wide variety of types of clinical studies. If the explanatory variable is continuous, the hazard ratio per 1-unit of change in the continuous explanatory variable is estimated by default in the PHREG procedure in SAS®. However, the estimates may not reflect a clinically meaningful change, especially for continuous and highly dispersed measurement. This paper introduces the hazard ratio per 'double' increase in continuous covariate of interest as another tool for comparing the two hazards. The author is convinced that this paper will be useful to any level of statistician, SAS programmer, or data analyst with an interest in medical follow-up studies and in general time-to-event studies.

PUBLISHED ARTICLES

Table. Published articles regarding hazard ratio per doubling of explanatory variable.

Study	Journal	Outcome	Explanatory	HR (95% CI)
Zhang 2006	J Am Soc Nephrol	Incident CVD event	IL-6	1.22 (1.11–1.34)
			High-sensitive CRP	1.24 (1.14–1.35)
Shafi 2012	Am J Epidemiol	All-cause mortality	β-trace protein	1.36 (1.09–1.69)
Shafi 2013	Diabetes Care	All-cause mortality	Fructosamine	1.96 (1.38–2.79)
			Glycated albumin	1.40 (1.09–1.80)
Kruzan 2016	BMC Nephrol	SCD	NTproBNP	1.27 (1.13–1.43)
			cTnI	1.17 (0.98–1.40)
Daya 2016	Am J Kidney Dis	Hospitalization (fracture)	AC ratio	1.10 (1.06–1.14)

HR = Hazard Ratio, CI = Confidence Interval, CVD = Cardiovascular Disease, SCD = Sudden Cardiac Death, IL-6 = Interleukin-6, CRP = C-reactive protein, NTproBNP = N-terminal pro-brain natriuretic peptide, cTnI = Troponin I, AC = Albumin-Creatinine.

Table presents a list of published articles [1-5] that presented hazard ratios per doubling of a continuous explanatory variable. For example, Kruzan and colleagues recently reported that the risk of sudden cardiac death (SCD) increased 27% with each 2-fold increase in NTproBNP (HR, 1.27 per doubling; 95% CI, 1.13-1.43; $p < 0.001$) [5].

HAZARD RATIO PER 1-UNIT INCREASE

Consider the basic proportional hazards model:

$$h(t \mid x) = h_o(t)exp(\beta x) \quad (1)$$

where $h_o(\mathrm{t})$ denotes the baseline hazard function.

The hazard rates would then be

$h(t \mid x = x_1) = h_o(t)exp(\beta x_1)$ and

$h(t \mid x = x_2) = h_o(t)exp(\beta x_2)$ for two different values of $x's$.

The ratio between these two hazard rates, or a hazard ratio (HR), would be

$$\begin{aligned} HR &= h(t \mid x = x_2) \,/\, h(t \mid x = x_1) \\ &= h_o(t)exp(\beta x_2) \,/\, h_o(t)exp(\beta x_1) \\ &= exp[\beta(x_2 - x_1)] \\ &= exp(\beta)\, if\ x_2 - x_1 = 1 \end{aligned}$$

$exp(\beta)$ can be interpreted as the hazard ratio for 1-unit increase in the explanatory variable, x.

Here is the pseudo SAS code for estimating the Cox regression model with the PROC PHREG procedure:

```
PROC PHREG DATA=mydata COVS(AGGREGATE);
    MODEL time*event(0) = x;
RUN;
```

The COVS(AGGREGATE) option is specified to compute the robust sandwich covariance matrix estimate [6].

HAZARD RATIO PER DOUBLE INCREASE

Now, consider lnx divided by $ln2$, instead of x, in equation (1).

Then we have

$$h(t \mid x) = h_o(t)\, exp\left(\beta \frac{lnx}{ln2}\right).$$

The hazard rates for two different values of $x's$ and hazard ratio would then be

$$h(t \mid x = x_1) = h_o(t)exp\left(\beta \frac{lnx_1}{ln2}\right) and$$

$$h(t \mid x = x_2) = h_o(t)exp\left(\beta \frac{lnx_2}{ln2}\right).$$

Then the ratio between these two hazard rates, or a hazard ratio, would be

$$
\begin{aligned}
HR = \; & h(t \mid x = x_2) \,/\, h(t \mid x = x_1) \\
= \; & h_o(t) exp\left(\beta \frac{lnx_2}{ln2}\right) \Big/ h_o(t) exp\left(\beta \frac{lnx_2}{ln2}\right) \\
= \; & exp\left(\frac{\beta}{ln2}(lnx_2 - \; lnx_1)\right) \\
= \; & exp\left(\frac{\beta}{ln2} ln \frac{x_2}{x_1}\right) \\
= \; & exp(\beta) \; if \; \frac{x_2}{x_1} = 2.
\end{aligned}
$$

Now, $\exp(\beta)$ can be interpreted as the hazard ratio per doubling of the explanatory variable, x.

Simple adjustment of the SAS code is needed as follows:

```
PROC PHREG DATA=mydata COVS(AGGREGATE);
    MODEL time*event(0) = x_adj;
    x_adj = log(x) / log(2);      /* log = log with base-e */
RUN;
```

CONCLUSION

Recent decades have seen tremendous applications of survival analysis in various academic fields. However, few have reported detailed information on computing hazard ratios per doubling of a continuous explanatory variable. This paper gently guides all SAS users—even those who have never used SAS—through step-by-step instructions of the doubling method. With the basic statistical theories along with the provided example SAS code, students and researchers will be able to use the doubling method, which can also be applied to any regression models having continuous, positive, and and/or dispersed explanatory variables.

REFERENCES

1. Zhang L, Kao WH, Berthier-Schaad Y, Liu Y, Plantinga L, Jaar BG, Fink N, Powe N, Klag MJ, Smith MW *et al*: Haplotype of signal transducer and activator of transcription 3 gene predicts cardiovascular disease in dialysis patients. *Journal of the American Society of Nephrology : JASN* 2006, 17(8):2285-2292.
2. Shafi T, Parekh RS, Jaar BG, Plantinga LC, Oberai PC, Eckfeldt JH, Levey AS, Powe NR, Coresh J: Serum beta-trace protein and risk of mortality in incident hemodialysis patients. *Clinical journal of the American Society of Nephrology : CJASN* 2012, 7(9):1435-1445.
3. Shafi T, Sozio SM, Plantinga LC, Jaar BG, Kim ET, Parekh RS, Steffes MW, Powe NR, Coresh J, Selvin E: Serum fructosamine and glycated albumin and risk of mortality and clinical outcomes in hemodialysis patients. *Diabetes care* 2013, 36(6):1522-1533.
4. Daya NR, Voskertchian A, Schneider AL, Ballew S, McAdams DeMarco M, Coresh J, Appel LJ, Selvin E, Grams ME: Kidney Function and Fracture Risk: The Atherosclerosis Risk in Communities (ARIC) Study. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2016, 67(2):218-226.
5. Kruzan RM, Herzog CA, Wu A, Sang Y, Parekh RS, Matsushita K, Hwang S, Cheng A, Coresh J, Powe NR *et al*: Association of NTproBNP and cTnI with outpatient sudden cardiac death in hemodialysis patients: the Choices for Healthy Outcomes in Caring for ESRD (CHOICE) study. *BMC nephrology* 2016, 17(1):18.
6. Allison PD: Survival analysis using SAS: A practical guide., 2nd edn. SAS Institute; 2010.

ACKNOWLEDGMENTS

This work is dedicated to my parents, Jeongja Han and Okgil Hwang. All I have and will accomplish are only possible due to their love and sacrifices. As always, most special thanks to Yun Kyoung Ryu for her advice and encouragement in getting me to finish this paper. She has been incredibly generous with her time in reviewing the draft and making many helpful suggestions. All remaining errors, omissions, and weaknesses are my sole responsibility.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Seungyoung Hwang, MS, MSE

Biostatistician, Department of Mental Health

Statistician, Division of Nephrology

DrPH Student, Department of Health Policy and Management

Johns Hopkins University

624 North Broadway, Hampton House 880

Baltimore, MD 21205

Email: seungyounghwang@gmail.com