Influence of Allocation Proportion of Intervention and Control on Results Analyzed Using the Cox Proportional Hazard Model: A Pilot Meta-Analysis Using Actual Clinical Trials

Soichi Takeishi MD, Tatsuo Inoue MD, Koichi Miyamura MD, PhD

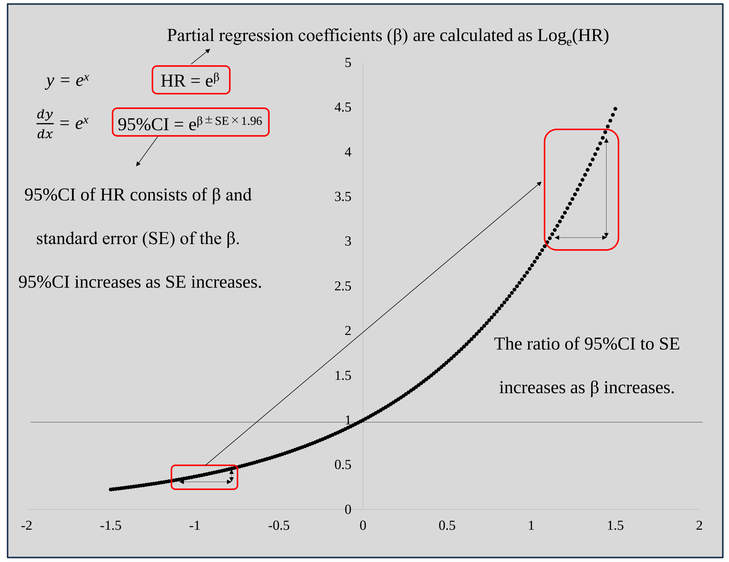
Infection Control Committee, Inuyama Chuo General Hospital

IDWeek 2024

P-1333

Background

- In reports assessing the effect of an intervention (I) on COVID-19–related endpoints using the Cox proportional hazard model, "allocation proportions of I and control (C)" vary.
- The effect of these allocation proportion on results analyzed using Cox regression in actual clinical trials is unknown.
- We conducted a pilot meta-analysis of clinical trials to investigate this effect.



Research design & Methods

- Articles published in The New England Journal of Medicine were included as part of a pilot meta-analysis if the following conditions were satisfied:
- 1. assessing endpoints related to COVID-19
- 2. using Cox regression.

- We referred to "upper limit of 95% confidence interval (CI) of hazard ratio (HR) (U95%CI) − lower limit of 95%CI of HR (L95%CI)" as the 95%CI range.
- Partial regression coefficients (β) were calculated as Log$_e$(HR)
- The standard error of β was estimated using ((Log$_e$ (U95%CI) – Log$_e$ (HR)) ÷ 1.96 + (Log$_e$ (HR) − Log$_e$ (L95%CI)) ÷ 1.96) ÷ 2, denoted as eSE.
- We calculated eSE ÷ an absolute value of β (eSE/|β|).

- The number of subjects (n) in an intervention group (nI) ÷ (nI + n in a control group (nC)) × 100 was termed "intervention proportion % (IP)", and nC ÷ (nI + nC) × 100 was termed "control proportion % (CP)".
- We calculated the absolute value of 40 − CP (|40 − CP|) and 40 – IP (|40 – IP|).

- For HR<1, "HR<1 adjusted group" (HR<1aG) retained the original metrics, while the "HR>1 adjusted group" (HR>1aG) used metrics calculated with the reciprocal of HR and its 95%CI (e.g. 0.50 (0.20-0.80) → 2.00 (1.25-5.00)).
- For HR>1, HR<1aG used metrics calculated with the reciprocal of HR and its 95%CI, while HR>1aG retained the original metrics.

Results and Discussions

We included 50 outcomes from 22 studies.

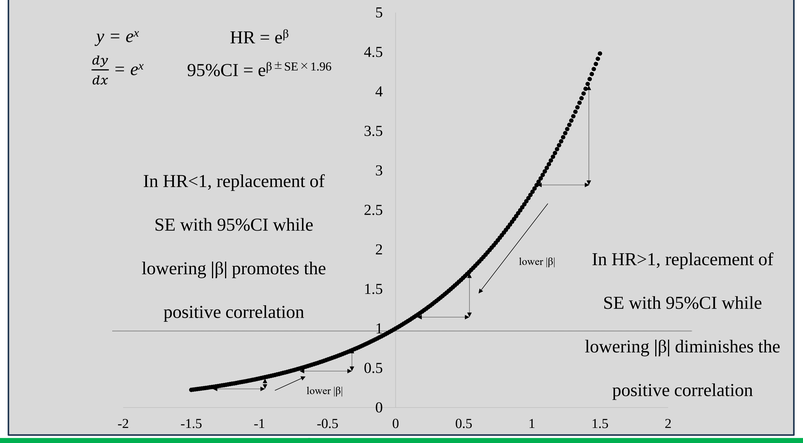
HR<1aG	95%CI range		β		eSE		eSE/|β|	
	r	p	r	p	r	p	r	p
|40-CP|	0.62	<0.001	0.10	0.50	0.36	0.01	0.63	<0.001
β					-0.59	<0.001		
HR>1aG	95%CI range		β		eSE		eSE/|β|	
	r	p	r	p	r	p	r	p
|40-IP|	0.01	0.93	-0.10	0.50	0.36	0.01	0.63	<0.001
β					0.59	<0.001		

Pearson product-moment correlation coefficient

- In HR<1aG, |40 − CP| correlated with the 95%CI range, whereas |40 – IP| did not correlate with the 95% CI range in HR>1aG.
- The positive correlation coefficient between |40 − CP| and β in HR<1aG and the negative correlation coefficient between |40 − IP| and β in HR>1aG were reversed.
- The positive correlation in HR<1aG and the negative correlation in HR>1aG between β and eSE were reversed.
- The correlation between |40 − CP| and eSE or eSE/|β| in HR<1aG and the correlation between |40 − IP| and eSE or eSE/|β| in HR>1aG were identical.

➢ Consideration regarding the correlation coefficient between |40 − CP| or |40 – IP| and 95%CI range

We consider the case where higher |40 − CP| or |40 − IP| causes relatively higher eSE despite lower |β|.



The needed knowledge regarding Cox proportional hazard model with a binary covariate

➢ When intervention and control interchange, HR and 95%CI after interchanging becomes the reciprocal of the HR and 95%CI before interchanging (e.g. 0.50 (0.20-0.80) → 2.00 (1.25-5.00)).

➢ When intervention and control interchange, positive and negative of β are reversed (e.g. 0.69 → -0.69)

➢ If intervention and control interchange, the SE is identical.

➢ SE reflects the credibility of β (higher SE means lower credibility)

➢ β mainly reflects the ratio of intervention to control

The reason why eSE/|β| was proposed

Relatively lower event incidence expands a confidence interval of ratio

\+ Takeishi, S et, al. The Lancet Regional Health - Western Pacific. 2023: 100761

Generally, SE increases as β increases

↓

Higher β (ratio) despite relatively lower event incidence makes a relationship that "SE increases as β increases"

When the influence of allocation proportion of intervention and control on the credibility of HR is evaluated, the characteristic that "SE increases as β increases" becomes bias.

↓

We proposed a metric, eSE/|β|, to evaluate the credibility of HR precisely.

Contact information

Soichi Takeishi, MD
Inuyama-city, Aichi,
484-8511, JAPAN
E-mail: souichi19811225@yahoo.co.jp
Phone: +81-568-62-8111
Fax: +81-568-62-9289

Conclusion

➢ The present study results may indicate that extremely biased allocation proportions of I and C diminish the credibility of HR.

➢ Replacing eSE/|β| with 95%CI range may not accurately assess this diminished credibility.