COX PROPORTIONAL HAZARD MODEL TO PREDICT A CARDIORENAL-RELATED EVENT RISK IN CONTROLLED TRIAL－PILOT META-ANALYSIS－

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Background

- Cox proportional hazard model (Cox) with a binary covariate (intervention [I] and control [C]) is widely used to assess the effect of treatment on reducing cardiorenal-related (CRr) event risk.
- Censoring and non-"proportional hazards" (PH) may affect reliability of the data analysed using Cox in controlled trials (CT).
- We conducted a pilot meta-analysis to elucidate the factors that lower reliability of data analysed using Cox in CT.

Research design & Methods

- We included articles that could be searched for free using PubMed for pilot meta-analysis.
- The following conditions were satisfied: 1. large randomized CT (n>100); 2. assessing CRr event risk; 3. using Cox, and 4. describing No. at Risk over the follow-up period.
- We evaluated all outcomes in one figure, which included the most important results of the studies.
- We divided the outcomes into two groups using a cutoff line of "hazard ratio (HR) = 1".
- We estimated the cumulative incidence (CuI) to the first decimal place using the Kaplan-Meier curves in the figure (referred to as eCuI).

  - ('No. at Risk. at the follow-up start time [0 year]' ('n') – No. at Risk. at the final follow-up year) ÷ n × 100: Total dropout rate (TDR)
  - TDR ÷ eCuI": TDR/eCuI
  - –Loge('1 – eCuI' for I) [Log'e', 'Napier's constant'] ÷ –Loge('1 – eCuI' for C): eHR
  - Absolute values of 'eHR – HR': |eHR – HR|
  - 'Upper limit of 95% confidence interval [CI] of HR (U95%CI)' – 'lower limit of 95%CI of HR' (L95%CI)": 95%CI range.
  - Partial regression coefficients (β) = Loge(HR).
  - Estimated standard error of β (eSE) was calculated using the following formula: ((Loge(U95%CI) – Loge(HR)) ÷ 1.96 + (Loge(HR) – Loge(L95%CI)) ÷ 1.96) ÷ 2

- Theoretically, an increased TDR/eCuI reflects increased censoring.
- eHR was proposed because "–Loge(cumulative survival rate functions [S(t)] for I in Cox) ÷ –Loge(S(t) for C in Cox)" is HR.
- Theoretically, an increase in |eHR – HR| quantitatively reflects enhanced non-PH.
- We also divided the outcomes in the HR<1 group into two groups using a cutoff line of "median of TDR/eCuI for C".

  - Primary endpoints

    Correlation between TDR/eCuI for C and 95%CI range in HR<1 group

    Correlation between |eHR – HR| and TDR/eCuI for C or 95%CI range in HR>1 group

Results and Discussions

We included 138 outcomes from 46 studies.

Characteristic	Total (138 outcomes in 46 studies)
n (Total)	6778 (3297-11139)
Final No. at Risk (Total)	633.5 (219.3-1722.8)
Follow-up, year	5 (4-8)
Significance, n (%)	73 (52.9)
Total dropout rate (Mean), %	89,7 (74.3-95.0)
Estimated cumulative incidence (Mean), %	11.8 (6.4-20)
Total dropout rate/Estimated cumulative incidence (Mean)	6.3 (3.8-10.1)
Intervention	
Diabetes treatment	76 (55.1)
Hypertension treatment	27 (19.6)
Hyperlipidemia treatment	21 (15.2)
Bariatric Surgery	8 (5.8)
Erythropoietin	6 (4.3)

Table 1: Patients characteristic
Data are shown as median (interquartile range)

Final No. at Risk: No. at Risk. at the final follow-up year
Significance: outcomes having statistical significance
Mean: (intervention + control) ÷ 2

HR<1 (n=113)	TDR/eCuI, control		|eHR - HR|		|β|		eSE		95%CI range	
	r	p	r	p	r	p	r	p	r	p
eCuI, intervention			0.27	0.004	-0.03	0.75	-0.34	<0.001	-0.33	<0.001
eCuI, control	-0.37	<0.001	0.21	0.02	0.33	<0.001	-0.14	0.15	-0.34	<0.001
TDR/eCuI, intervention			0.02	0.87	0.11	0.23	0.53	<0.001	0.53	<0.001
TDR/eCuI, control			0.02	0.83	-0.03	0.76	0.44	<0.001	0.55	<0.001
|eHR - HR|					0.10	0.31	0.13	0.17	0.08	0.39
|β|							0.53	<0.001	-0.02	0.82
eSE/|β|							0.31	<0.001	0.65	<0.001

Table 2: The correlations between metrics related to Cox in HR<1 group
r: Pearson product-moment correlation coefficient

The correlation data and consideration enclosed with a solid line and the same color are associated.
The correlation data in HR<1 and HR>1 groups and considerations enclosed with a dotted line and the same color are associated.

The ratio of 'cumulative incidence for intervention' to 'that for control' increased due to "high cumulative incidence for control", rather than "low cumulative incidence for intervention".

Censoring may have expanded 95%CI range through increasing SE.

Increased |β| raised SE of β
↓
Theoretically, lower incidence with constant difference increases ratio (|β|), and increases SE

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Lower event incidence leading to disadvantageous results may increase censoring for control in HR>1.

The influence of censoring on the shape of KM curves was not so large enough to affect nonproportional hazards when HR < 1 where censoring for control promoted the advantageous ratio.

Censoring may have strongly affected nonproportional hazards when HR > 1 because censoring for control may have chronologically resisted the disadvantageous ratio.

(n=56)	eSE		(n=57)	eSE	
TDR/eCuI control < median	r	p	TDR/eCuI control > median	r	p
|β|	0.75	<0.001	|β|	0.4	0.002

Table 3: The correlations between |β| and eSE r: Pearson product-moment correlation coefficient

Increased censoring diminishes the correlation between |β| and SE
↓
Increased censoring generates high SE despite low |β|

An increase in values raises variability in values → In HR<1, increased eCuI raised |eHR – HR|

In HR>1, "Lower incidence → more censoring → increased |eHR – HR|"

In HR>1, censoring for control raising |eHR – HR| may have increased to lower the disadvantageous ratio in high |β|

Increased SE compared to |β| expanded 95%CI range
↓
Increased SE compared to |β| = lower incidence with constant ratio (|β|) increases SE = expanded 95%CI range due to increased SE

Increased censoring for control may have caused
"decreased disadvantageous |β|" and "decreased SE due to increased incidence" simultaneously.

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Brief Summary

It may be that censoring in control promoted the ratio and this may be read from 95%CI.

HR>1 (n=25)	TDR/eCuI, control		|eHR - HR|		|β|		eSE		95%CI range	
	r	p	r	p	r	p	r	p	r	p
eCuI, intervention			-0.44	0.03	-0.32	0.12	-0.54	0.005	-0.50	0.01
eCuI, control	-0.62	<0.001	-0.44	0.03	-0.38	0.06	-0.55	0.005	-0.53	0.007
TDR/eCuI, intervention			0.66	<0.001	0.39	0.05	0.61	0.001	0.57	0.003
TDR/eCuI, control			0.65	<0.001	0.51	0.01	0.53	0.007	0.55	0.004
|eHR - HR|					0.78	<0.001	0.69	<0.001	0.79	<0.001
|β|							0.52	0.01	0.74	<0.001
eSE/|β|							-0.02	0.93	-0.07	0.74

Table 4: The correlations between metrics related to Cox in HR>1 group
r: Pearson product-moment correlation coefficient

Increased |β|, namely disadvantageously increased ratio, was associated with increased censoring for control. The association was stronger than the case of censoring for intervention.

Increased nonproportional hazards results in expanded 95%CI range through increased SE.

Brief Summary

Increased censoring for control may promote nonproportional hazards, resulting in decreased credibility of data.

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Conclusion

- Increased censoring and non-PH may lower reliability of data analysed using Cox in CT.
- One of the reasons why the positive correlation between |β| and eSE diminished more in high censoring group than in low censoring group may be that, theoretically, increased censoring is sure to increase CuI, except that the number of events is 0.