INVESTIGATING A QUANTITATIVE METRIC FOR ESTIMATING PROPORTIONAL HAZARDS IN TIME-TO-EVENT OUTCOMES –A SIMULATION STUDY USING REAL-WORLD DATA

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Background

- Cox proportional hazard model (Cox) with a binary covariate is used widely to assess the effect of intervention (I) on cardiorenal event risks.
- As Kaplan-Meier (KM) curves of I and control (C) approximate proportional hazards (PH), quality of data analyzed using Cox becomes high.
- Quantitative methods for assessing PH are unknown.
- If PH can be quantitatively estimated from published KM curves of I and C, data reliability is easier to assess.
- We conducted a simulation study using real-world data for quantitative evaluation of PH.

Research design & Methods

- We used glucose levels (GL) measured at 15-minute intervals using continuous glucose monitoring (CGM: FreeStyle Libre Pro) as time-to-event data.
- This data was selected for two reasons. Firstly, there is no censoring; secondly, observation periods and timepoints are unified.
- We analyzed GL for 100 “outpatients with Type 2 diabetes” (pT2D), measured by CGM over 24-h for 13 days (from 0 AM on Day 2 to 0 AM on Day 15 [CGM attachment: Day 1]).
- The pT2D did not change their treatments throughout the CGM observation period.
- We analyzed cumulative survival rates [S(t)] using Cox [S(t)Cox] and KM method [S(t)KM] for 13 endpoints where time to event was expected to be delayed by I, compared to C.
- Observations were done at all GL measurement.
- The GL value at each of these timepoints is estimated to be identical to the GL values in the preceding 1–14 minutes for calculating metrics proposed later.
- We defined “–Loge(S(t)KM for I) [Log‘e’, ‘Napier's constant’] ÷ – Loge(S(t)KM for control [C])” as “e hazard ratio” (eHR).
- We proposed a quantitative metric, “absolute value of difference between eHR and HR” (|eHR–HR|) to estimate PH for time-to-event outcomes.
- “ΔLoge(–Loge(S(t)Cox)) [C – I]” (Δlog–logS(t)Cox) is constant at every observation time because Cox has a fundamental PH. Hence, we proposed a metric, absolute value of coefficient of variation (CV) of 18720 (60×24×13) "ΔLoge(–Loge(S(t)KM)) [C – I] at one-minute intervals [Δlog–logS(t)KM]" (|CV|Δlog–logKM) for estimating PH.
- Since we thought lower CV of 18720 “Δ‘1 – S(t)KM’ [C – I] at one-minute intervals [ΔKM]” (CVΔKM) better satisfy PH, we proposed a metric, CVΔKM, to visually assess PH from KM curves.
- Corresponding with the concept of Restricted Mean Survival Time (RMST), we propose a metric, RMST related index (RMSTrI), as sum of 18720 ΔKM. Gregson J, et al. J Am Coll Cardiol. 2019; 74: 2102-2112.

➢ Primary endpoints

A correlation between |eHR – HR| and |CV| of Δlog–log (KM).

Results and Discussions

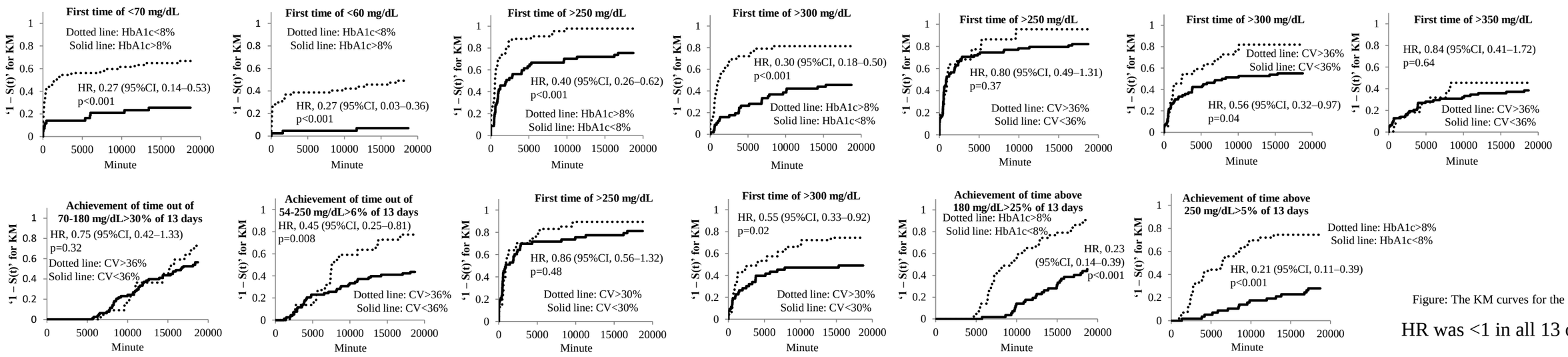

Figure: The KM curves for the 13 endpoints.

HR was <1 in all 13 outcomes.

Characteristic	Values
N (Male / Female)	100 (60 / 40)
Age, years	69.5 ± 13.4
BMI, kg/m^2	24.2 ± 4.1
HbA1c, %	8.0 ± 1.5

Table 1: The characteristics of patients providing the CGM data

Data are shown as mean ± standard deviation.

BMI, body mass index; HbA1c, hemoglobin A1c

Response variable	Binary covariate (Intervention / Control)	HR	|1-HR|	eHR	|eHR-HR|	|CV|Δlog–logKM, %	CVΔKM, %	RMSTrI
First time of <70 mg/dL	HbA1c>8% / HbA1c<8%	0.27	0.73	0.27	0.00	11.06	10.19	7209.82
First time of <60 mg/dL	HbA1c>8% / HbA1c<8%	0.11	0.89	0.11	0.00	7.32	12.95	6652.06
First time of >250 mg/dL	HbA1c<8% / HbA1c>8%	0.40	0.60	0.37	0.03	13.74	13.07	4910.10
First time of >300 mg/dL	HbA1c<8% / HbA1c>8%	0.30	0.70	0.36	0.07	21.22	17.61	7658.46
First time of >250 mg/dL	CV<36% / CV>36%	0.80	0.20	0.56	0.24	65.05	60.79	1996.85
First time of >300 mg/dL	CV<36% / CV>36%	0.56	0.44	0.47	0.09	45.32	36.44	4058.29
First time of >350 mg/dL	CV<36% / CV>36%	0.84	0.16	0.80	0.04	143.56	99.27	1080.91
Achievement of time out of 70-180 mg/dL>30% of 13 days	CV<36% / CV>36%	0.75	0.25	0.64	0.11	751.81	791.86	153.01
Achievement of time out of 54-250 mg/dL>6% of 13 days	CV<36% / CV>36%	0.45	0.55	0.39	0.06	82.32	78.40	3301.91
First time of >250 mg/dL	CV<30% / CV>30%	0.86	0.14	0.74	0.11	69.96	59.05	1678.78
First time of >300 mg/dL	CV<30% / CV>30%	0.55	0.45	0.49	0.06	46.77	35.08	3669.81
Achievement of time above 180 mg/dL>25% of 13 days	HbA1c<8% / HbA1c>8%	0.23	0.77	0.26	0.02	59.47	44.44	5568.10
Achievement of time above 250 mg/dL>5% of 13 days	HbA1c<8% / HbA1c>8%	0.21	0.79	0.24	0.03	23.72	29.79	7615.51

Figure 2: The metrics for the 13 endpoints.

CV: coefficient of variation

|eHR–HR| correlated to |CV|Δlog–logKM.

|CV|Δlog–logKM correlated to CVΔKM.

|1–HR| correlated to RMSTrI.

r=0.62, p=0.02

r=0.98, p<0.001

r=0.86, p<0.001

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Conclusion

- Using |eHR–HR| as a quantitative metric, PH may be estimated from published KM curves.
- Catching variability of difference in S(t)KM at the same timepoint between I and C visually, PH may be estimated.
- Area between KM curves of I and C may reflect |1–HR|.