Beyond Kaplan-Meier & Cox
A Competing Risk Approach to Peritonitis in Malaysia

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To ensure the reproducibility of this research, the analysis and write-up were completed entirely within the R environment

Introduction

Peritonitis is an important medical event for patients who undergo peritoneal dialysis (PD). Most time-to-event (TTE) studies on peritonitis did not consider competing risk events. A competing risk is defined as the event that precludes the occurence the event of interest (Gooley et al. 1999). E.g. premature death or technique failure that precludes the occurence of peritonitis.

Objectives

1. Evaluate the cause-specific and subdistribution hazard of peritonitis
2. Describe the risk factors associated with the hazards of first peritonitis episode

Methods

A prospective cohort of incident PD patients `(n=1149)` between January 2014 and December 2018 was included in the analysis. Competing risk regression models based on cause-specific and subdistribution hazards of first peritonitis were discussed.

The event of interest was `first peritonitis`. Competing risk events were composite events of `death` and `technique failure` prior to the first peritonitis. The CI function for individual competing risk event was calculated using the Fine&Gray model (subdistribution hazards) and the Cox proportional hazard model (cause-specific hazards).

To avoid overfitting the model, we considered 9 baseline covariates: age, gender, race, diabetes as primary renal disease, requirement for assistance to complete daily PD, dialysis centre, time since first PD (months), time since diagnosis of ESRF, and brand of PD product.

We further fit multiple subdistribution hazard models using the "backward" selection process and select the model with the lowest BIC value.

Results

Overall time-to-first-peritonitis in the whole cohort

There were a total of 1149 patients in this cohort, with 418 episodes of first peritonitis reported. KM analysis indicated that the median time to first peritonitis was 39.9 months.

Cause-specific hazard

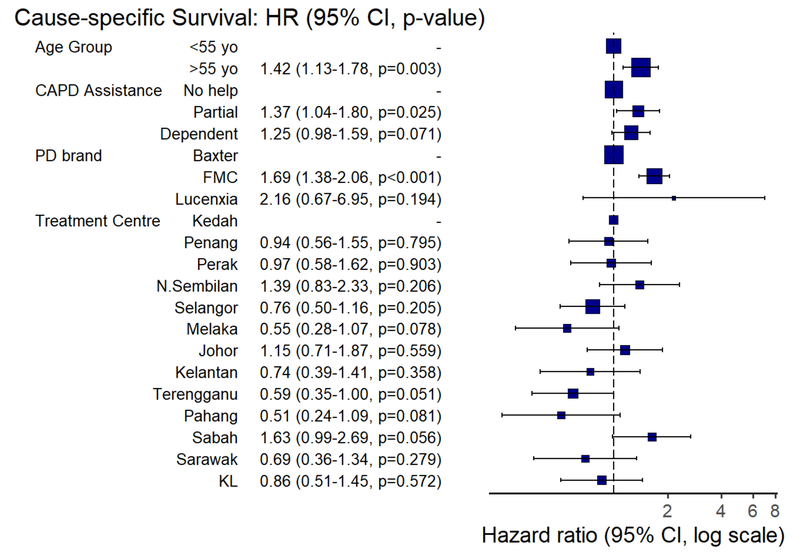
Cox proportional hazard (CPH) regression was used to evaluate the cause-specific hazard of peritonitis. Univariate analysis indicates that *Age group*, *Assistance to complete CAPD*, *PD brand*, *Diabetes as primary renal disease*, and *Treatment centre* were significant covariates (p<0.1) and should be included in the subsequent multivariate analysis. A subsequent multivariate CPH analysis indicated showed that *Age group* `(HR: 1.43; 95% CI: 1.13-1.78)`, *Partial Assistance for CAPD* `(HR: 1.37; 95% CI: 1.04-1.80)`, and the *FMC brand* `(HR: 1.69; 95% CI 1.38-2.06)` were significant risk factors for first peritonitis.

Subdistribution hazard

Competing risk analysis using the Fine & Gray model suggested that, when compared to the Baxter PD product, FMC product reported a higher rate of peritonitis occurence in the entire cohort `(HR: 1.69; 95% CI: 1.38-2.06)`.

The side-by-side comparison of univariable CPH, multivariable CPH, and competing risk regression was illustrated in the table below:

Dependent: Survival		all	HR (DSS CPH multivariable)	HR (competing risks multivariable
Age Group	<55 yo	395 (34.4)	•	•
	>55 yo	754 (65.6)	1.42 (1.13-1.78, p=0.003)	1.26 (1.00-1.59, p=0.052)
CAPD Assistance	No help	621 (54.0)	•	•
	Partial	181 (15.8)	1.37 (1.04-1.80, p=0.025)	1.29 (0.97-1.70, p=0.076)
	Dependent	347 (30.2)	1.25 (0.98-1.59, p=0.071)	1.08 (0.84-1.38, p=0.560)
PD brand	Baxter	723 (62.9)	•	•
	FMC	421 (36.6)	1.69 (1.38-2.06, p<0.001)	1.71 (1.40-2.09, p<0.001)
	Lucenxia	5 (0.4)	2.16 (0.67-6.95, p=0.194)	2.87 (1.08-7.63, p=0.035)
Treatment Centre	Kedah	80 (7.0)	•	•
	Penang	70 (6.1)	0.94 (0.56-1.55, p=0.795)	1.02 (0.61-1.71, p=0.940)
	Perak	76 (6.6)	0.97 (0.58-1.62, p=0.903)	0.88 (0.53-1.48, p=0.640)
	N.Sembilan	58 (5.0)	1.39 (0.83-2.33, p=0.206)	1.45 (0.85-2.46, p=0.170)
	Selangor	331 (28.8)	0.76 (0.50-1.16, p=0.205)	0.73 (0.48-1.12, p=0.150)
	Melaka	53 (4.6)	0.55 (0.28-1.07, p=0.078)	0.53 (0.27-1.04, p=0.065)
	Johor	97 (8.4)	1.15 (0.71-1.87, p=0.559)	1.04 (0.63-1.71, p=0.880)
	Kelantan	34 (3.0)	0.74 (0.39-1.41, p=0.358)	0.76 (0.40-1.42, p=0.390)
	Terengganu	117 (10.2)	0.59 (0.35-1.00, p=0.051)	0.52 (0.31-0.88, p=0.015)
	Pahang	42 (3.7)	0.51 (0.24-1.09, p=0.081)	0.42 (0.20-0.87, p=0.020)
	Sabah	68 (5.9)	1.63 (0.99-2.69, p=0.056)	1.55 (0.92-2.60, p=0.099)
	Sarawak	42 (3.7)	0.69 (0.36-1.34, p=0.279)	0.68 (0.35-1.32, p=0.260)
	KL	81 (7.0)	0.86 (0.51-1.45, p=0.572)	0.89 (0.52-1.52, p=0.670)



Parsimonous model

Using the forward method and the Bayesian information criterion (BIC), the most parsimous competing risk model has *PD brand* as the sole covariate.

Discussion

In the presence of competing risk, we had two choices to fit the survival model. The cause-specific hazard model (multivariate CPH) suggested that older age, partial assistance to perform CAPD, and PD product from FMC could increase the rate of peritonitis in patients who were still event-free. This finding corresponds to our previous studies (Ong et al. 2017).

Although the variable *treatment centre* showed significance, our model selection process suggested that only the *PD brand* should be included in the final model (most parsimonous). The model suggested that a switch from Baxter to FMC PD product was associated with 69% increase in the subdistribution hazard of peritonitis. However, we cautioned that this association warrants further confirmation.

References

Gooley, T. A., W. Leisenring, J. Crowley, and B. E. Storer. 1999. "Estimation of Failure Probabilities in the Presence of Competing Risks: New Representations of Old Estimators." *Stat Med* 18 (6): 695–706. https://doi.org/10.1002/(sici)1097-0258(19990330)18:6<695::aid-sim60>3.0.co;2-o.

Ong, Loke Meng, Chin Chin Ch'ng, Hong Chin Wee, Premaa Supramaniam, Hadzlinda Zainal, Bak Leong Goh, Sunita Bavanandan, Lily Mushahar, Lai Seong Hooi, and Ghazali Ahmad. 2017. "Risk of Peritoneal Dialysis-Related Peritonitis in a Multi-Racial Asian Population." *Perit Dial Int* 37 (1): 35–43. https://doi.org/10.3747/pdi.2015.00141.