NHIS Ilsan Hospital

Time-varying exposure effect for adjusting time-varying confounding on competing risks

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INTRODUCTION

BACKGROUND: On competing risks data, regression models for an event of interest are 1) Cox's regression model of cause-specific hazard considering the competing event as censoring and 2) Fine and Grays' regression model of subdistribution hazard for the cumulative incidence function in existing the competing event. However, there are some challenges to directly apply both regression models on observational data, such as dealing with time-varying exposure and confounders. Cox's regression model of cause-specific hazard can be naturally extended for time-varying covariates, while Fine and Gray's regression model has a limitation to work with time-varying covariates. There is no proper methods to apply time-varying exposures for adjusting time-varying confounders on competing risks.

OBJECTIVE: To estimate the time-varying exposure effect for cumulative incidence of main disease of interest, adjusting for the time-varying confounding in existing the competing disease

METHOD

Proposed method

Step 1: Estimating Marginal Structure Model (MSM) for adjusting time-varying confounding

Step 2: Estimating the cause-specific hazard ratio with weights of MSM

Step 3: Estimating the subdistribution hazard ratio using relationship formula

To avoid potential bias from time-varying confounding

We suggest the marginal structure model (MSM) for the cause-specific hazard and the subdistribution hazard of the time-varying exposure, adjusting for the time-varying confoundings via the relationship between the cause-specific hazard and the subdistribution hazard, derived by Beyersmann and Schumacher (2007)[1].

We conducted the simulation to exam the performance of the proposed method compared to previous methods and applied the real data analysis.

Simulation process

1. Generation
   - A. Generating an observed cohort of 500 subjects with repeated data with time-varying exposure, confounders and events (event of interest and one competing event) as the following scenario
     - ORs=2.0 for the relationship between a confounder and an exposure
     - Subdistribution HRs=2.0 of the exposure for the event of interest
     - Subdistribution HRs=0.5 or 2.0 of the confounder for the event of interest
   - B. Reiterating 500

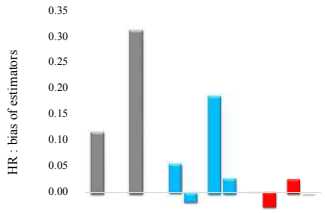
2. True value
   Establishing truth values from the deterministic potential outcomes based on all observation data (500 subjects in a cohort)×(500 cohorts) and their expected outcomes assuming the other exposures (500 subjects in a cohort)×(500 cohorts)[2]
   - A. Calculating the true overall survival rates of any events
   - B. Calculating the true cause-specific HRs
   - C. Calculating the true cumulative incidence rates
   - D. Calculating the true subdistribution HRs using formula

3. Estimation
   Estimating parameters in each observed cohort, reiterating 500
   - A. Estimating the overall survival rates of any events
   - B. Estimating cause-specific HRs and 95% C.I.
   - C. Estimating cumulative incidence rates
   - D. Estimating subdistribution HRs using formula
   - E. Estimating 95% bootstrap C.I. of subdistribution HRs using bootstrapping (1000 resamples)

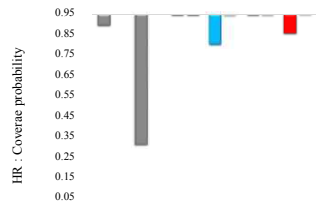
4. Comparison
   - A. Comparing the mean bias of cause-specific HR estimators and coverage probability (the proportion of time the 95% C.I. covers the true value) for KMI, multiple regression and the proposed method
   - B. Comparing the mean bias of suhdistribution HR estimators and coverage probability for KMI, multiple regression, and proposed method

RESULTS

SIMULATION: In the simulation result, the proposed method showed the reduction in the bias of the estimators and close to the nominal level of 0.95 in coverage probabilities, as compared to the standard multiple regression or KMI(Kaplan-Meier multiple imputation) method in subdistribution HR for cumulative incidence function.



	0.5* KMI(R function)	2.0* KMI(R function)	0.5* Multiple regression	2.0* Multiple regression	0.5* Proposed method	2.0* Proposed method
subdistribution HR	0.116	0.313	0.054	0.187	-0.001	0.025
cause-specific HR			-0.018	0.029	-0.028	0.000



	0.5* KMI(R function)	2.0* KMI(R function)	0.5* Multiple regression	2.0* Multiple regression	0.5* Proposed method	2.0* Proposed method
subdistribution HR	0.898	0.318	0.968	0.808	0.956	0.860
cause-specific HR			0.960	0.946	0.954	0.952

Figure 1. Bias of estimators and coverage probabilities (HR of exposure : 2.0, * : HR of confounder)

REAL DATA ANALYSIS

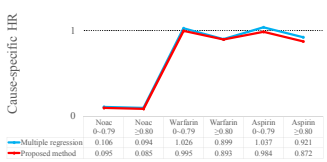
SUBJECT: 5,796 subjects with cerebral infarction disease defined as ICD-10(I63,I64,I69, G463-G468,I678,I679) with MRI or CT at the baseline (2004~2007) in 2% randomly selected subjects from the Korean nationwide data containing medical care claims data (N=48,222,537)

OUTCOME: Main event of interest: cerebral infarction recurrence, competing risk event: all cause death (from diagnosis date to 2015).

EXPOSURE: Time-varying adherence (PDC≥80%), non-adherence (PDC<80%) of antiplatelet therapy (Noac, Warfarin, or Aspirin) during 90 days or no therapy

CONFOUNDINGS: Time-varying previous bleeding and patient histories such as gender, age, diabetes, hypertension, hyperlipidemia, economic status, CHADS2-VASc, or end-stage renal disease

RESULTS: Adherence (PDC≥80%) of antiplatelet therapy decreases about 15~30% of the recurrence of the cerebral infarction for cumulative incidence, compared to no antiplatelet therapy. In proposed method, the recurrence of the cerebral infarction increased to non-adherence (PDC<80%) of Warfarin.



	Noac 0-0.79	Noac ≥0.80	Warfarin 0-0.79	Warfarin ≥0.80	Aspirin 0-0.79	Aspirin ≥0.80
Multiple regression	0.106	0.094	1.026	0.899	1.037	0.921
Proposed method	0.095	0.085	0.995	0.893	0.984	0.872

	Noac 0-0.79	Noac ≥0.80	Warfarin 0-0.79	Warfarin ≥0.80	Aspirin 0-0.79	Aspirin ≥0.80
Multiple regression	0.761	0.494	0.904	0.730	0.871	0.653
Proposed method	1.004	0.716	1.101	0.831	0.991	0.688

Figure 2. HR of adherence and non-adherence in outcome with recurrence of the cerebral infarction, compared to no therapy

CONCLUSION

CONCLUSION: We proposed the competing risks data analysis with the time-varying exposure for adjusting time-varying confounding on observational data. Our simulation results presented a proper method to estimate the effect of time-varying exposure from marginal structure model on competing risks.

1. Beyersmann J., Schumacher M. Time-dependent covariates in the proportional subdistribution hazards model for competing risks, Biostatistics, 2008:9:765-776.
2. Catherine R. Lesko, Bryan Lau. Bias Due to Confounders for the Exposure–Competing Risk Relationship, Epidemiology (Cambridge, Mass.), 2017.