DukeNUS Medical School | National Cancer Centre Singapore | MSR5

Controlling unmeasured confounding and bias in evaluation of treatment effectiveness using real-world data, with application to palliative care

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Background

- Observational studies of palliative care (PC) are prone to confounding by indication – patients referred to PC are often sicker.
- Comprehensive measurement of all confounders is practically impossible.
- The Prior Event Rate Ratio (PERR) method leverages each patient's outcome events before treatment initiation to control bias from measured or unmeasured confounders.

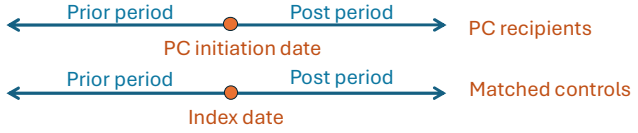
Objectives

- Propose and evaluate a statistical model for recurrent event analysis to control for (unmeasured) time-constant confounding and bias arising from unobserved heterogeneity.
- A real-world evaluation of the effect of PC on emergency department (ED) visits among stage IV cancer patients.

PERR Method

- PERR method controls measured or unmeasured time-constant confounding by using event rate ratio in a prior period as reference.
- The date of PC initiation is used to define prior and post periods in the PC recipients; it is also used to generate an index date to define the prior and post periods in matched controls.

PERR Framework



- The original PERR method uses Cox model to separately analyze first outcome event in the prior period and post period and use a ratio of hazard ratios to control confounding. We call this estimate of treatment effect PERR Cox:

$$PERR\ Cox = \frac{HR_{Post}}{HR_{Prior}},$$

where HR_{Prior} and HR_{Post} are hazard ratios of event rates between groups in the prior and post periods, respectively.

New PERR Model

- We reformulate the PERR method to become one single time-to-recurrent event analysis model with a treatment-by-period interaction term based on the Andersen-Gill (AG) model [1]:

$$\lambda_i(t) = \lambda_0(t)\exp(\beta_1 trt_i + \beta_2 post_i + \beta_3 \times trt_i \times post_i), \qquad (1)$$

where $\lambda_0(t)$ is unspecified baseline hazard at time t, $trt_i = 1$ if patient i is ever treated during the observation period, and $trt_i = 0$ otherwise, $post_i = 1$ if person-time is in the post-period, and $post_i = 0$ otherwise.

- In equation (1), β_3 is the new PERR estimate of intervention effect. We call this as the PERR AG.
- The Cox model for analysis of time-to-first event is biased in the presence of unobserved heterogeneity. In contrast, the AG model for recurrent time-to-event data is unaffected by unobserved heterogeneity. PERR Cox and PERR AG inherit the properties of the Cox and AG models, respectively.

Simulation

- Time to recurrent events follows an increasing Weibull hazard function with time-varying treatment indicator, time-constant confounders and unobserved heterogeneity from Normal$(0, \sigma_\omega^2)$.
- Simulation shows PERR AG has unbiased mean estimates of treatment effect and accurate coverage probability (CP) of 95% confidence interval (CI); PERR Cox is biased except when there is no unobserved heterogeneity.

Table 1: Simulation results, by three levels of unobserved heterogeneity (σ_ω^2) and true treatment effect (hazard ratio) is 0.5.

	PERR Cox		PERR AG	
σ_ω^2	Estimate	CP(%)	Estimate	CP(%)
0	0.518	93.8	0.514	94.1
0.5	0.537	92.3	0.509	95.7
1.0	0.562	82.8	0.511	93.0

Palliative Care Study

- 7144 patients were diagnosed with stage IV cancer at National Cancer Centre Singapore between Jan 2019 and Dec 2022, followed up to Jul 2023 [2]. Among them, 1499 received PC during the study period.
- We applied 1:3 matching with replacement to match approximately 3 non-PC recipients to each PC recipient. The PERR analysis cohort included 5948 patients and 2157 ED visits.
- Table 2 shows that PC group had higher ED visit rate before starting PC than non-PC group (rate ratio in prior period=5.65/0.45=12.56).
- Table 3 shows that PC was associated with 3.2-fold increase of ED visit rate as per standard time-to-recurrent event analysis, but 38% reduction in ED visit rate from our proposed PERR AG analysis.

Table 2: Incidence in PC and non-PC recipients in prior and post periods

	Non-PC (N=4473)			PC (N=1475)		
Period	ED visits	Person-years	Incidence	ED visits	Person-years	Incidence
Prior	297	654.4	0.45	1101	195.0	5.65
Post	297	733.1	0.41	462	145.9	3.17

Table 3: Treatment effect estimates

	HR	95% CI	P-value
Time-to-event regression *	3.20	(2.83, 3.63)	<0.001
PERR AG	0.62	(0.51, 0.77)	<0.001

* Time-to-recurrent event analysis using AG model with PC as a time-varying exposure variable and with adjustment for measured time-constant covariates.

Conclusions

- Our proposed method combines the strengths of PERR method and Andersen-Gill model in controlling unmeasured time-constant confounders and bias arising from unobserved heterogeneity.
- The sharp contrast of different hazard ratio estimates obtained from regression with covariates adjustment versus PERR AG indicates the advantage of controlling unmeasured confounding by PERR AG.

Acknowledgement

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References

[1] Ma et al, SIM 2026. DOI: 10.1002/sim.70441
[2] Yang et al, JPSM 2026. DOI: 10.1016/j.jpainsymman.2026.04.612