MI-CRE Methods Group journal club: Prevalent new-user cohort design

Malcolm Gillies

https://github.com/mbg-unsw/pnuc

1 July 2021

main@3571d89 2021-07-01

Today's paper

Practice of Epidemiology

Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis

Tanja Tran and Samy Suissa*

* Correspondence to: Samy Suissa, Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research, Jewish General Hospital, 3755 Côte-Sainte-Catherine, H-411, Montreal, Quebec H3T 1E2, Canada (e-mail: samy.suissa@mcgill.ca).

Initially submitted March 26, 2020; accepted for publication October 27, 2020.

- T. Tran and S. Suissa. **Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis.** *American Journal of Epidemiology*, 190(5):928–938, May 2021. doi:10.1093/aje/kwaa242.

Talk outline

- Paper background
- Prevalent new-user cohort method in detail
- Adjusting for informative censoring
- Results
- What does the PNUC method estimate?
- Loose ends

main@3571d89 2021-07-01

What is the paper about?

- Question: Are PPIs efficacious in idiopathic pulmonary fibrosis?
- Data: UK linked GP and hospital data (CPRD-GOLD/HES/ONS), $n = 2944$
- Outcomes: All-cause mortality, respiratory death, hospitalisation
- Covariates: Demographics, comorbidity, medicines (all time-varying)
- Compare results from three different study designs

Idiopathic Pulmonary Fibrosis (IPF)

- Progressive scarring of the lungs, cause unknown
- Average life expectancy after diagnosis about four years
- Pirfenidone (2008) and nintedanib (2014) slow progression
- Proton pump inhibitors also guideline recommended (weak evidence)
- Contention: PPI effects seen in earlier studies are due to bias

Review: Active comparator new-user cohort design

- Confounding by indication (inactive comparator)
- Healthy adherer bias (prevalent users)

Why *prevalent* new-user?

- *i.e.* Compare those staying on old tx with switchers to new
- Increase sample size if few treatment-naive patients
- Better external validity e.g. disease progression
- Key feature: conditioning on length of exposure

Prevalent new-user cohort design step by step

1. Defining the base cohort
2. Forming exposure sets
3. Estimating the propensity score
4. Matching and forming the analysis cohort
5. Estimating the causal effect

main@3571d89 2021-07-01

Defining exposure sets and estimating the propensity score

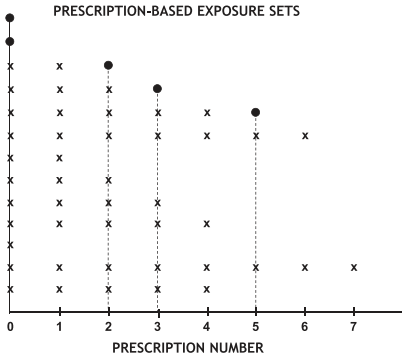


Figure 3. Depiction of a base cohort formed of 13 subjects with prescription-based exposure sets defined by the number of comparator drug prescriptions (**x**) before the first study drug prescription (●) was given

Suissa et al. (2017)

Matching

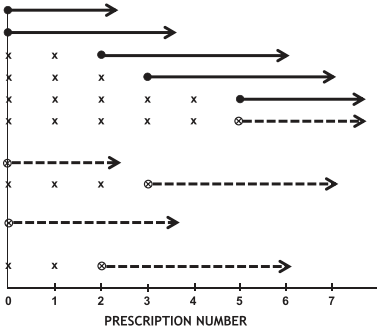


Figure 4. Depiction of the final prevalent new-user comparative cohort with comparator drug subjects matched to study drug subjects on the number of comparator drug prescriptions (x) before the first study drug prescription (●) was given, with the arrows indicating the follow-up period for outcomes

Suissa et al. (2017)

Informative censoring

- In this study, “prevalent user” = IPF patient *not* treated with PPI
- Follow-up of prevalent users is censored if PPI treatment starts
- Starting PPI = patient is still alive (but sicker?)

Adjusting for informative censoring

- Option 1: Restriction
  - exclude PPI ever users from prevalent cohort
- Option 2: Weighting
  - use inverse probability of censoring weights (IPCW)
  - estimate from logistic regression model (*à la* propensity)

Results 1

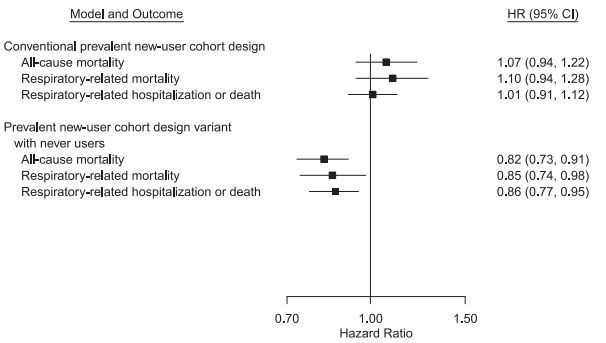


Figure 3. Hazard ratios (HRs) for respiratory-disease–related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence intervals (CIs).

Marginal Structural Cox Model

- All patients followed from IPF diagnosis
- Exposure and covariates assessed in each person-month
- Inverse probability of treatment weights (IPTW)
- Inverse probability of censoring weights (IPCW)
- Estimation with weighted time-dependent Cox model

Results 2

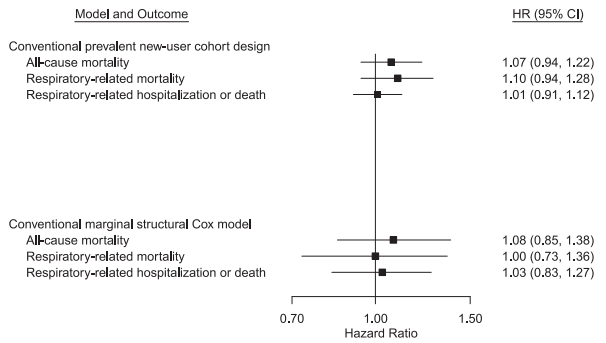
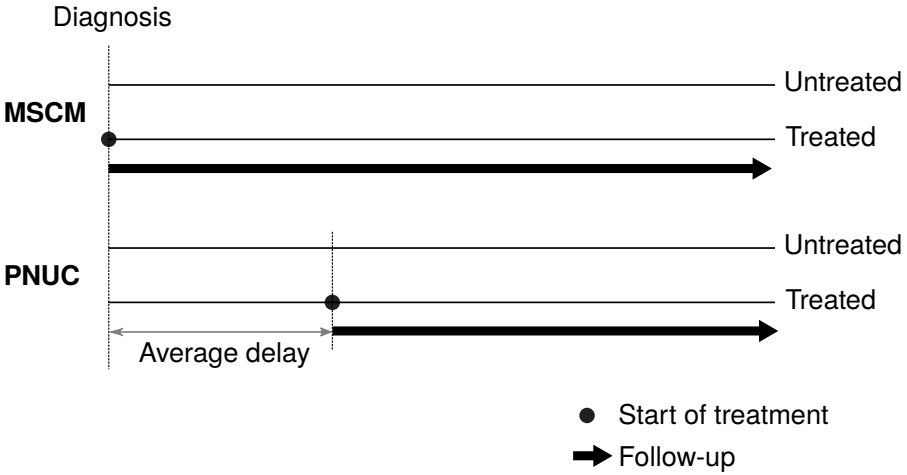


Figure 3. Hazard ratios (HRs) for respiratory-disease–related hospitalization and mortality associated with proton pump inhibitor use (compared with no use) obtained using 3 different study designs in a cohort of patients with idiopathic pulmonary fibrosis, United Kingdom, 2003–2016. Bars, 95% confidence intervals (CIs).

Estimands


Diagnosis
MSCM
Untreated
Treated
PNUC
Untreated
Treated
Average delay
Start of treatment
Follow-up

PNUC sub-cohorts

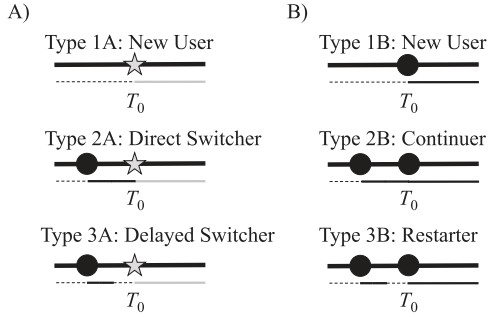


Figure 1. Infographic showing treatment histories of various types of initiators of treatment A and users of B. Panel A includes the initiators of treatment A (types 1A–3A) and panel B includes the 3 corresponding individuals taking treatment B that would be "ideal" counterfactual contrasts for types 1A–3A. Gray stars represent prescriptions for A, while black circles represent prescriptions for B. Below each set of prescriptions is a secondary timeline showing time with no treatment (dashed black), time treated with A (gray), and time treated with B (solid black).

Webster-Clark et al. (2020)

main@3571d89 2021-07-01

Loose ends

- Matching with/without replacement
- Conditioning on length of exposure vs entire history
- Positivity and matching
- Estimating the propensity score
- See also: `https://pharmacoepi.unc.edu/wp-content/uploads/sites/6788/2020/12/Webster-Clark_Michael_PNU.pdf`

Discussion

- Have you used the prevalent new-user cohort design or the marginal structural Cox model approach? If so, please tell us about it.
- Would you use either of these methods for your current research interests? What do you see as the barriers to using them?

References

S. Suissa, E. E. M. Moodie, and S. Dell'Aniello. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiology and Drug Safety*, 26(4):459–468, 2017. doi: 10.1002/pds.4107. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/pds.4107.

T. Tran and S. Suissa. Comparing New-User Cohort Designs: The Example of Proton Pump Inhibitor Effectiveness in Idiopathic Pulmonary Fibrosis. *American Journal of Epidemiology*, 190(5):928–938, May 2021. doi: 10.1093/aje/kwaa242. URL https://doi.org/10.1093/aje/kwaa242.

M. Webster-Clark, R. K. Ross, and J. L. Lund. Initiator Types and the Causal Question of the Prevalent New-User Design: A Simulation Study. *American Journal of Epidemiology*, page kwaa283, Dec. 2020. doi: 10.1093/aje/kwaa283. URL https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwaa283/6043913.