Matched Design with Re-entry and Missingness for Comparative Effectiveness in Membranous Nephropathy

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Background

- Clinical trials comparing treatment efficacy in rare diseases such as membranous nephropathy (MN) can be limited by short follow-up and small sample sizes
- MN is an autoimmune glomerular disease and a frequent causes of nephrotic syndrome — yet no FDA-approved treatments for MN currently exist!
- Existing methods for generating high-quality evidence from observational data often focus on big data and EHR settings

AIM: demonstrate how statistical methods can be combined to reliably compare treatment efficacy in rare disease settings using observational data

Methods

Study Sample and Design

- Cure Glomerulonephropathy (CureGN) is an ongoing prospective observational cohort study of patients with biopsy-proven MN among other glomerular diseases
- Individuals starting rituximab (RTX) or calcineurin inhibitors (CNI) at least 6 mos. after any previous treatment exposure were eligible, **allowing sequential re-entry** as participants could be eligible more than once

Statistical Analysis Framework

1. **Multiple Imputation (MI):** incomplete observations were multiply imputed and retained
2. **Propensity-Score Matching:** propensity scores were (1) estimated from a logistic GEE (*in our example, an exchangeable correlation structure was assumed*) to account for possible repeated inclusions within individual participants (due to the re-entry) and then (2) used in 1:1 optimal matching without replacement with exact matching on treatment history
3. **Analog to Per-Protocol Analysis:** individuals were artificially censored if they started a different treatment during follow-up and **inverse-probability-of-censoring weights [IPCW; Eq (1) and (2)]** were applied
   - *NOTATION:* (a) $L_{k,i}$ denotes a set of time-varying covariates at time k for individual i; (b) $\bar{A}_{(0,\,k-1),i}$= R denotes adherence to the RTX protocol from time 0 up to time $k-1$, $\bar{A}_{(0,\,k-1),i}$ = C denotes adherence to the CNI protocol; (c) t^1 denotes the time of the first recorded change in the set L, and $\underset{\smile}{t}$ denotes the time of the most recent change in the set L before time t

RTX Arm IPCW:

$$SW_i^R(t) = \prod_{j=t^1}^{\underset{\smile}{t}} \frac{Pr\left(A_j = R \middle| L_{0,i},\, \bar{A}_{(0,\,j-1),i} = R\right)}{Pr\left(A_j = R \middle| L_{j,i},\, \bar{A}_{(0,\,j-1),i} = R\right)} \qquad (1)$$

CNI Arm IPCW:

$$SW_i^C(t) = \prod_{j=t^1}^{\underset{\smile}{t}} \frac{Pr\left(A_j = C \middle| L_{0,i},\, \bar{A}_{(0,\,j-1),i} = C\right)}{Pr\left(A_j = C \middle| L_{j,i},\, \bar{A}_{(0,\,j-1),i} = C\right)} \qquad (2)$$

   - An **analog to intention-to-treat (ITT) analysis** based only on the initiated treatments was also considered
4. **Robust Survival Analyses**

➢ All estimates were obtained separately in each imputed dataset then pooled using **Rubin's rules** (Rubin, 1987):

Pooled Estimate of a Parameter Q: $\bar{Q} = \frac{1}{m}\sum_{i=1}^{m}\widehat{Q_i}$ | *Average of Imputed Dataset Variances:* $\bar{U} = \frac{1}{m}\sum_{i=1}^{m} U_i$

Estimated Total Variance: $T = \bar{U} + \left(1 + \frac{1}{m}\right)B$ | *Between Imputation Variance:* $B = \frac{1}{m-1}\sum_{i=1}^{m}\left(\hat{Q}_i - \bar{Q}\right)^2$

➢ Estimators of U_i needed to account for **possible repeated inclusions** within individual participants AND **matching**

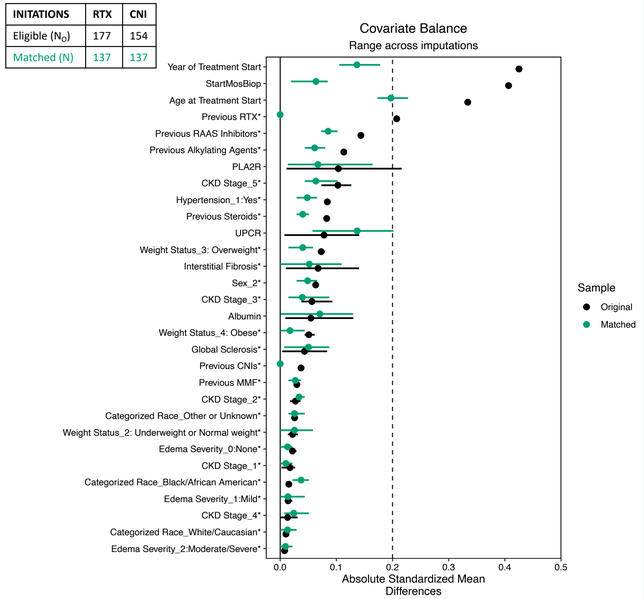
- **Hazard ratios (HRs)** with robust confidence intervals accounting for *multilevel non-nested clustering* (Austin and Cafri, *Stat Med,* 2020) were estimated and pooled from Cox proportional hazards models
- **Restricted mean survival times (RMSTs)** with bootstrap confidence intervals obtained using the 'MI Boot' method (Schomaker and Heumann, *Stat Med*, 2018) were pooled over imputations

5. **Sensitivity Analyses** considered matching with replacement and addressed varying treatment durations

Results

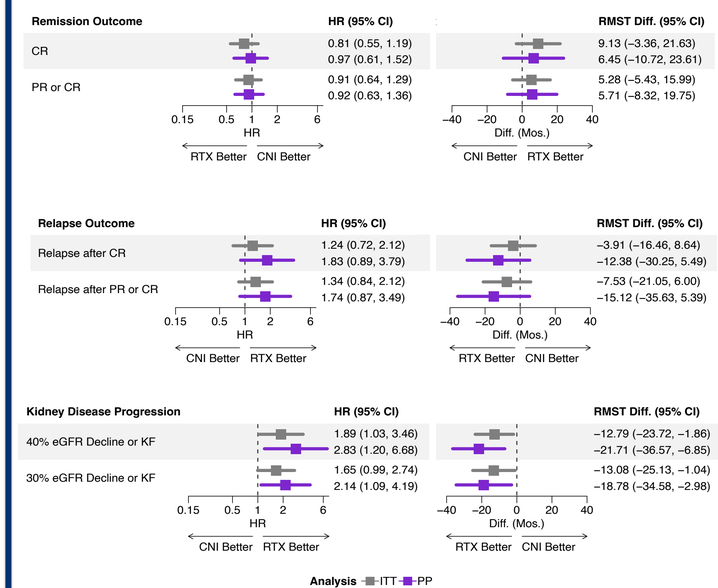
Figure 1. Love-Plot for 1:1 Matches

INITATIONS	RTX	CNI
Eligible (N_0)	177	154
Matched (N)	137	137



*Mean differences between categorical variables were not standardized. Average values across imputations are denoted by points, and intervals denote ranges across imputations.

Figure 2. Forest Plot of HRs and RMSTs for 1:1 Matched Analysis



Outcome Notation: CR = Complete Proteinuria Remission (UPCR < 0.3 g/g); PR = Partial Proteinuria Remission (0.3 g/g < UPCR < 3.5 g/g with 50% reduction); KF= kidney failure (replacement therapy or eGFR<15);

Discussion

- Several analytic approaches — ITT vs. PP, primary and secondary definitions of outcomes, different matching schemes, two metrics for effect estimation, and analyses that limited treatment duration—demonstrated **similar results**, increasing confidence in the findings
- RTX tended to have lower rates of relapse and was significantly more effective for preventing long-term disease progression
- The short-term proteinuria remission and relapse **results generally align with the findings of the 24-month MENTOR trial** (Fervenza et al., *NEJM*, 2019), with some differences attributable to the use of a more pragmatic study sample
- This study demonstrates how a matched design combined with sequential re-entry and MI can be applied to observational data to generate high-quality evidence about comparative treatment effectiveness in MN and other rare disease contexts in the absence of clinical trials
- Simulation studies exploring the benefits and limitations of *sequential re-entry in longitudinal observational studies with active comparators* are underway

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