

Incorporating Inverse Probability of Censoring Weighting (IPCW) into the OHDSI CohortMethod Workflow

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A brief intro to CohortMethod (and Strategus)

- R package within HADES ecosystem for **new-user cohort studies** for OMOP data
- Framework behind many previous OHDSI network studies!



Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis

Marc A Suchard, Martijn J Schuemie, Harlan M Krumholz, Seng Chan You, RuiJun Chen, Nicole Pratt, Christian G Reich, Jon Duke, David Madigan, George Hripcsak, Patrick B Ryan

JAMA Ophthalmology | Original Investigation

Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

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Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes

A Multinational, Federated Analysis of LEGEND-T2DM



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Challenge: addressing informative censoring

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Comparative Cardiovascular Effectiveness of Glucagon-Like Peptide 1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors in Diabetes Mellitus

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Reviewers were concerned about informative censoring

- Statistical survival analysis methods (ex, Kaplan-Meier, Cox PH model) rely on **non-informative censoring**
  - i.e., censoring is independent of the outcome of interest conditional on observed covariates

Reviewers were concerned about informative censoring

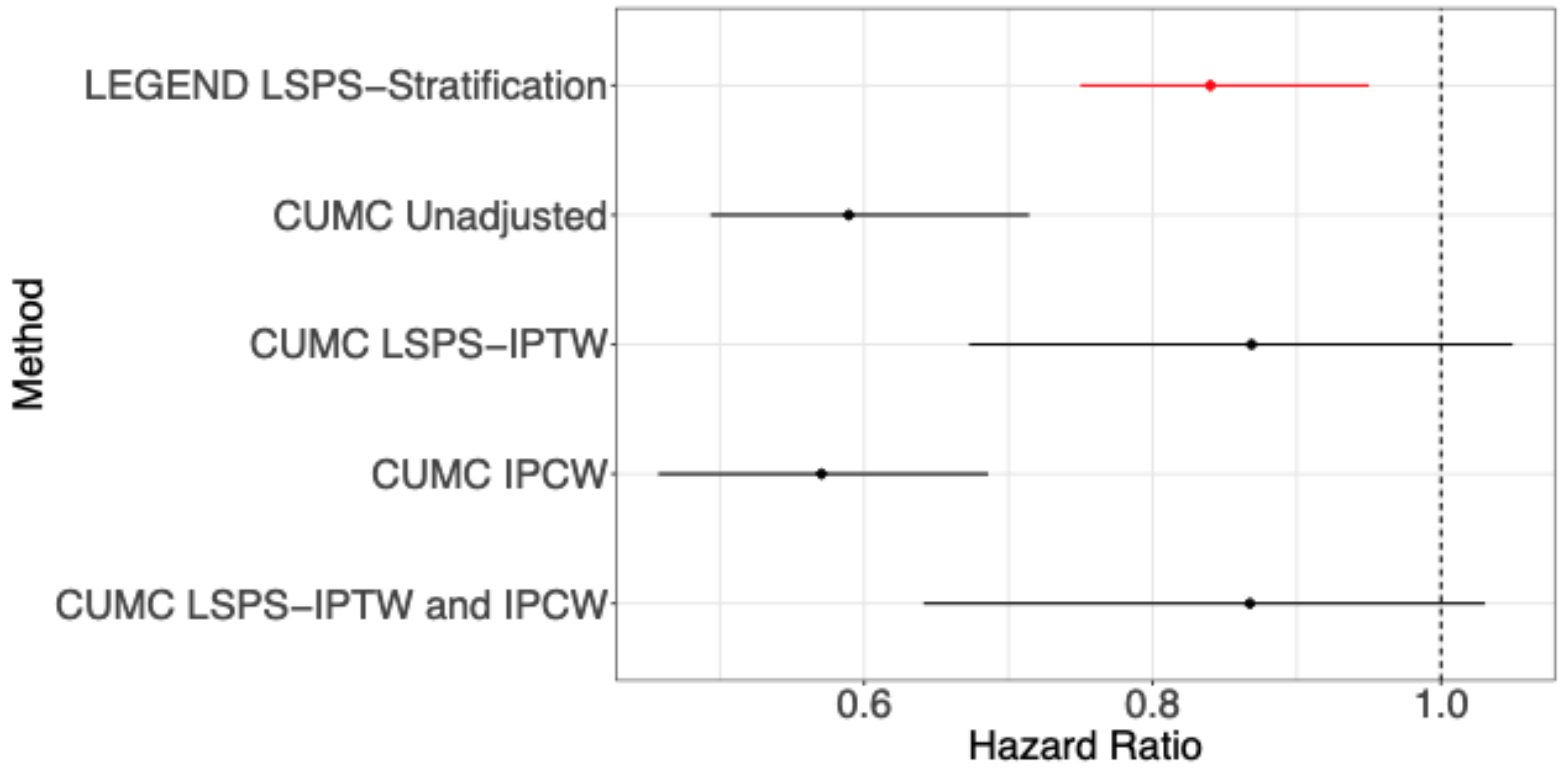
- If censoring reason (ex: dropping out of the study, treatment discontinuation, etc.) is related to the outcome (*informative censoring)*, that can violate key assumptions of survival analysis models
- One possible solution: Inverse Probability of Censoring (IPCW)

An aside: when is IPCW adjustment necessary?

- Our recent simulation study showed that, in presence of informative censoring, IPCW-adjustment improves survival curve estimates, but **only improves bias and coverage of HR when the strength of informative censoring additionally differs by treatment group**

An aside: when is IPCW adjustment necessary?

- One example from the LEGEND-HTN study (ACEi vs Thiazide Diuretics on the risk of AMI):



Adjusted for:

Confounding

Nothing

Confounding

Censoring

Confounding + Censoring

An aside: when is IPCW adjustment necessary?

When Does IPCW Help? Simulation and Real-World Evidence on Censoring Adjustment in Survival Analysis

Hsin Yi Chen[1], Tara V. Anand[1], Linying Zhang[2], George Hripcsak[1]

Recently accepted by *Statistical Methods in Medical Research*!

Back to the JACC paper review…

We recognize and really appreciate the importance of pre-specification. However, as noted by the statistical editor, we think that conducting IPCW-based analyses would be very important to improving the robustness of the paper. We think that this approach could be presented as a post-hoc sensitivity analyses.

- Reviewers really wanted IPCW!

Current CohortMethod Workflow

CohortGenerator and CohortMethod

1 **Generate cohorts**

Target, comparator and outcome cohorts

2 **Propensity score model**

Fit Large-scale PS model to get inverse-probability-of-treatment **(IPTW)** weights:

$$w_i^{Ps} = 1/\pi_i \text{ or } 1/(1-\pi_i)$$

where π_i is the probability of receiving treatment

3 **Outcome Model**

Fit outcome model with weights w, i.e.

$$h(t|A) = h_0(t) \cdot exp(\beta A)$$

$$HR = exp(\beta)$$

Currently implemented in Strategus!

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Fit outcome model with weights w, i.e.

$$h(t|A) = h_0(t) \cdot exp(\beta A)$$

$$HR = exp(\beta)$$



add fitting censoring model for censoring weights here

Proposed IPCW Implementation

Cohort Generation & PS
CohortGenerator and CohortMethod

1 Generate cohorts
Target, comparator and outcome cohorts

2 Propensity score model
Fit Large-scale PS model to get inverse-probability-of-treatment **(IPTW)** weights:

$$w_i^{Ps} = 1/\pi_i \text{ or } 1/(1-\pi_i)$$

where π_i is the probability of receiving treatment

Proposed IPCW Steps
FeatureExtraction · Cyclops

3 Censoring Cox Model
Fit large-scale penalized Cox model to get the inverse-probability of remaining uncensored **(IPCW)** weights:

$$w_i^{c} = 1 / G_i(T_i)$$

Where $G_i(T_i)$ is the probability of remaining uncensored at time t

4 Combine Weights
$$w_i(t) = w_i^{Ps} * w_i^{c}(t)$$

Outcome Modeling
CohortGenerator and CohortMethod

5 Outcome Model
Fit outcome model with weights w, i.e.

$$h(t|A) = h_0(t) \cdot exp(\beta A)$$

$$HR = exp(\beta)$$

Code: **github.com/ohdsi-studies/ExploringCensoringWeights**

We responded to the reviewer's request using OHDSI tools ☺

Supplementary Table 99: Comparing analytic results from four variant methods with IPCW (for censoring) and/or IPTW (for confounding). We summarize hazard ratio estimates and 95% confidence intervals for 3-point MACE and 4-point MACE between new-users of semaglutide and empagliflozin, across three databases, CCAE, Clinformatics and OptumEHR. Cox = Cox proportional hazards model; IPCW = inverse probability censoring weights; IPTW = inverse probability treatment weights.

	CCAE	Clinformatics	OptumEHR
3-point MACE			
Unadjusted Cox	0.87 (0.67, 1.14)	0.69 (0.56, 0.84)	0.67 (0.48, 0.93)
Cox with IPCW	0.84 (0.63, 1.11)	0.65 (0.53, 0.81)	0.66 (0.47, 0.92)
Cox with IPTW	0.98 (0.68, 1.40)	1.05 (0.82, 1.34)	1.06 (0.73, 1.55)
Cox with IPCW + IPTW	0.91 (0.62, 1.34)	0.99 (0.75, 1.29)	1.07 (0.72, 1.57)
4-point MACE			
Unadjusted Cox	0.76 (0.62, 0.94)	0.74 (0.64, 0.84)	0.60 (0.48, 0.76)
Cox with IPCW	0.75 (0.61, 0.93)	0.70 (0.61, 0.81)	0.60 (0.47, 0.76)
Cox with IPTW	0.88 (0.67, 1.15)	1.06 (0.89, 1.25)	0.90 (0.68, 1.19)
Cox with IPCW + IPTW	0.87 (0.65, 1.17)	1.01 (0.84, 1.22)	0.88 (0.66, 1.18)

Existing OHDSI Infrastructure allows for customization

- Support packages within the HADES suite (Cyclops, FeatureExtraction, etc) makes customization of OHDSI workflows possible!

Thank you!

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