Application of a Quasi-Experimental Study Design to Pharmacoepidemiology: An Evaluation of Immune Checkpoint Inhibitor Therapy and Cholangitis Using Real-World Data as a Case Study

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Introduction

- Unmeasured confounding is a key threat to validity of observational studies using real-world data (RWD)
- Causal statistical methods (such outcome model adjustment, propensity score matching, or g-computation) have the potential to yield biased results as they rely on the availability of data on confounders, which is often limited in RWD sources
- Quasi-experimental studies (such as instrumental variables, natural experiments, or difference-in-difference [DID] studies) account for unmeasured confounding by virtue of their design, provided certain assumptions are met. However, there is limited evidence within RWD that demonstrates unmeasured confounding and evaluates its attenuation through the application of quasi-experimental study designs

Objectives

We used immune checkpoint inhibitor (ICI)-related cholangitis as a case study to:

- demonstrate unmeasured confounding in conventional observational study designs despite the application of causal statistical methods
- evaluate the application of a DID study design for its feasibility and potential to attenuate unmeasured confounding.

Methods

- Data: PharMetrics®, from 2011 to 2022.
- Study population & follow up (FU):
  - Non-ICI cohort: an ICI-eligible cancer cohort not treated with ICIs, followed over their 2 most recent years of cancer diagnosis (labelled as yr.1 and yr. 2)
  - ICI cohort: an ICI-treated cohort followed from 12 months before (labelled as yr. 1) to 12 months after ICI initiation (labelled as yr. 2).
- Study designs compared:
  - Independent cohort: non-ICI cohort, yr. 2 vs ICI cohort, yr. 2
  - Pre-post cohort: ICI cohort, yr. 1 vs. ICI cohort, yr. 2
  - DID: included both cohorts and yrs.; effect estimate derived using an interaction term between cohort and yr. of FU.
- Outcome: Cholangitis identified using ICD codes.
- Statistical analysis: unadjusted and adjusted Cox proportional hazards regression models

Results

- Of the 511,403 patients included, 54% were male; mean (SD) age was 63 (12) years (Table 1).
- Incidence rates of cholangitis were higher at baseline (pre-treatment) in the ICI cohort compared with the non-ICI cohort and increased over time in the absence of ICI-therapy (Table 2)
- While ICI-therapy was not associated with cholangitis (HR: 1.10 [0.89-1.37]) in the DID study, a statistically significant association was observed in the cohort study and in the pre-post cohort study, even after adjustment by inverse probability of treatment weighting (Table 3).

Table 1. Demographics and clinical characteristics of the study population

	Non-ICI cohort N = 446,308	ICI-treated Cohort N = 65,095
Age (years), Mean (SD)	62.7 (11.8)	62.4 (11.2)
Sex, N (%)		
Female	208,065 (46.6%)	26,799 (41.2%)
Insurance type, N (%)		
Commercial	318,247 (71.3%)	48,782 (74.9%)
Medicaid	4,774 (1.1%)	550 (0.8%)
Medicare	104,792 (23.5%)	15,366 (23.6%)
Other	1,879 (0.4%)	231 (0.4%)
Missing	16,616 (3.7%)	166 (0.3%)
US region, N (%)		
Midwest	117,868 (26.4%)	18,371 (28.2%)
Northeast	101,265 (22.7%)	10,489 (16.1%)
South	157,414 (35.3%)	26,127 (40.1%)
West	66,991 (15.0%)	9,939 (15.3%)
Missing	2,770 (0.6%)	169 (0.3%)
ICI regimen, N (%)		
Nivolumab	NA	17,660 (27.1%)
Nivolumab + ipilimumab	NA	6,851 (10.5%)
Pembrolizumab	NA	30,692 (47.1%)
Ipilimumab	NA	2,831 (4.3%)
Atezolizumab	NA	6,793 (10.4%)
Other ICI regimens	NA	258 (0.4%)
Cancer type*, N (%)		
Colorectal	152,538 (34.2%)	3,565 (5.5%)
Gastric	19,715 (4.4%)	4,237 (6.5%)
Hepatocellular	14,011 (3.1%)	3,558 (5.5%)
Lung	88,915 (19.9%)	32,053 (49.2%)
Malignant melanoma	97,487 (21.8%)	13,715 (21.1%)
Renal	76,928 (17.2%)	8,698 (13.4%)
Charlson comorbidity score, Mean (SD)	3.4 (2.6)	7.1 (2.0)
Any use of chemotherapy or targeted therapy, N (%)	60,127 (13.5%)	4,584 (7.0%)

*Some patients may have more than one diagnosis

Table 2. Cholangitis incidence rates, and hazard ratios from the DID model

	Number of patients	Number of events	IR (95% CI) per 1000 person-years	HR (95% CI)	P
Non-ICI cohort Yr. 1 (ref)	446,308	739	1.67 (1.55, 1.80)		
Non-ICI cohort Yr. 2	440,188	1,681	3.86 (3.68, 4.05)	2.32 (2.13, 2.53)	<0.001
ICI cohort pre-treatment	65,095	174	2.68 (2.31, 3.10)	1.60 (1.35, 1.89)	<0.001
ICI cohort post-treatment	64,921	276	5.26 (4.67, 5.91)	**Isolated effect of ICI treatment:** 1.10 (0.89, 1.37)*	0.368*

DID: Difference in difference; IR: Incidence rate; HR: Hazard ratio
*HR and p-value correspond to the interaction term.

Table 3. Effect estimates by study design and covariate adjustment

Study design	Statistical model	Effect estimate (95% CI)	P
Independent cohort	Unadjusted analysis	HR: 1.87 (1.62, 2.15)	<0.001
	Adjusted analysis*	HR: 1.62 (1.39, 1.88)	<0.001
	IPTW*	ATET^: -4.8 (-5.7, -3.9)	<0.001
Pre-post cohort	Unadjusted analysis	HR: 2.32 (1.89, 2.85)	<0.001
	Adjusted analysis**	HR: 2.32 (1.89, 2.85)	<0.001
Difference in difference[α]	Unadjusted analysis	HR: 1.10 (0.89, 1.37)	0.368
	Adjusted analysis**	HR: 1.10 (0.89, 1.37)	0.375

IPTW: Inverse probability of treatment weighting. *Adjusting for baseline covariates; **Adjusting for chemo- or targeted cancer therapy use as time-varying covariates; ^ATET: Average treatment effect in the treated, interpretation: in the ICI-treated cohort, average time to cholangitis is estimated to be 4.8 months less than had ICI-treated patients not been treated with ICIs. [α]Key assumption: rate of increase in cholangitis incidence over time is similar between the ICI cohort and the non-ICI cohort.

Conclusions

- Unadjusted and adjusted results from the independent cohort study and the pre-post cohort study showed evidence of unmeasured/residual confounding that was attenuated by the DID study design.
- A DID study design is feasible and practical for drug safety studies using real-world data and has the potential to mitigate bias in the absence of exchangeability.