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## BACKGROUND

- Nonresponse to patient-reported outcome measures is common and can vary over time in real-world longitudinal research.
- Such missingness can introduce bias that not only compromises the generalizability of study findings but may also lead to misinterpretation.
- In a case study examining the association between symptom assessment completion and chemotherapy (CTX) discontinuation, we proposed using inverse probability weighting (IPW) to address the time-dependent bias introduced by nonresponse.

## METHODS

- This retrospective cohort study used routinely collected patient-reported symptom data and electronic health records (EHRs) from the Mass General Brigham (MGB) health system. MGB has implemented the routine collection of patient-reported outcome measures (PROMs) for clinical care wholly within its EHR.<sup>1</sup>
- At MGB GI cancer clinics, the Patient-Reported Outcome (PRO) version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE<sup>®</sup>) are collected from all clinic visits. Patients with scheduled appointments are asked to complete PRO-CTCAE one week before their visit through the EHR patient portal. Those who do not complete the symptom assessment in advance are offered tablets to do so during their clinic visit.
- Between 01/2019 and 01/2024, we identified adult patients with GI cancers who (1) received CTX and (2) completed any symptom assessment within 15 days of CTX initiation (i.e., the start of a new CTX episode), or at one, two, or three months following a new CTX episode.
- The primary outcome was discontinuation due to toxicity within 90 days of initiation. Using the Fine-Gray model to account for competing risks of death and progression, we examined the association between discontinuation and number of completed assessments over time.
- To address the time dependent nonresponse bias associated with disease severity, treatment, and prior completion, we constructed IP weights for each follow-up time point.

## CONSTRUCTION OF INVERSE PROBABILITY WEIGHT

The probability of completion is calculated at each time point. At CTX initiation, the probability of completion ( $p_0$ ) is 1. For any subsequent time point  $i$ , the overall probability of completion ( $P_i$ ) is the cumulative product of the conditional probabilities of completion from time 0 through time  $i$ , i.e.  $p_0, \dots, p_i$ . The formula for calculating  $P_i$  is shown in Formula 1:

$$P_i = P_{i-1} \cdot p_i = \left( \prod_{t=0}^{i-1} p_t \right) \cdot p_i \quad (\text{Formula 1})$$

For each time point, the weight ( $W_i$ ) is calculated as the inverse of the probability of completion ( $P_i$ ) (Formula 2). The final weight was retained for each individual and adjusted in the analysis.

$$W_i = \frac{1}{P_i} \quad (\text{Formula 2})$$

The probability of completion at each time point post chemotherapy initiation was modeled using age, sex, race, level of education, cancer site, cancer stage, concurrent immunotherapy, concurrent radiation therapy, use of 5-fluorouracil, use of oxaliplatin, use of gemcitabine, comorbidity, symptom score at CTX initiation, and prior completion.

## MAIN FINDINGS

	Subdistribution hazard ratio (95%CI)	
	Unweighted	Weighted
<b>Overall sample</b>		
<b>Number of completion</b>	0.49 (0.25 – 0.95)	0.70 (0.44 – 1.12)
<b>Age groups</b>		
≤ 64 years	0.72 (0.42 – 1.24)	0.99 (0.64 – 1.52)
> 64 years	0.27 (0.07 – 0.99)	0.31 (0.08 – 1.17)
<b>Comorbidity</b>		
CCI = 0	0.62 (0.37 – 1.06)	0.80 (0.50 – 1.27)
CCI ≥ 1*	-	-
<b>Cancer stage</b>		
I, II, & III	0.63 (0.34 – 1.17)	0.85 (0.49 – 1.47)
IV	0.33 (0.10 – 1.10)	0.58 (0.31 – 1.06)
<b>Cancer site</b>		
Pancreatic cancer	0.50 (0.17 – 1.43)	0.79 (0.41 – 1.55)
Other cancers	0.48 (0.24 – 0.97)	0.65 (0.36 – 1.15)

Notes: We controlled age, sex, race, level of education, cancer site, cancer stage, concurrent immunotherapy, concurrent radiation therapy, use of 5-fluorouracil, use of oxaliplatin, use of gemcitabine, comorbidity, symptom score at treatment initiation. CCI: Charlson comorbidity index. \*: Model was not converged due to small sample size.

## RESULTS

- Among 1,178 patients, 67% completed assessments at baseline and during follow-up.
- The unweighted model without adjustment for nonresponse bias found significant relationship between number of symptom assessment completion and discontinuation. In the weighted model accounting for nonresponse bias, completing additional symptom assessments after CTX initiation was associated with a lower risk of discontinuation; however, this relationship was not statistically significant.

## CONCLUSIONS

- More frequent completion of patient-reported symptom assessment post CTX initiation was associated with a lower risk of early discontinuation in practice.
- Our findings highlight the importance of recognizing and addressing time-dependent nonresponse bias in real-world longitudinal research using patient-reported outcome measures. We advocate for the application of appropriate methods, such as IPW, to manage such bias and improve the validity of study findings.

## REFERENCE

- Liu JB, Kaplan RS, Bates DW, Edelen MO, Sisodia RC, Pusic AL. Mass General Brigham's Patient-Reported Outcomes Measurement System: A Decade of Learnings. NEJM Catalyst. 2024;5(7)doi:10.1056/cat.23.0397.

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**ETHICS REVIEW:** This study was approved by the Dana-Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board (IRB protocol number: 25-048).

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