Population-level Impact of CAR-T Approval on Diffuse Large B-Cell Lymphoma Mortality: A CDC WONDER, Age-Stratified, Difference-in-Differences Analysis

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Introduction

Anti-CD19 CAR-T therapy was first licensed for relapsed/refractory DLBCL in Oct 2017. Its population-level mortality impact in the US has remained uncertain.

Objectives

To estimate post-approval changes in age-adjusted DLBCL mortality using age-stratified difference-in-differences (DiD) with external lymphoma controls.

Data Source

- CDC WONDER mortality, 1999–2023; outcome = underlying-cause deaths coded ICD-10 C83.3 (DLBCL).
- Comparison cohorts: PTCL (C84; no CAR-T), MCL (C83.1; CAR-T 2020), FL (C82; CAR-T 2021).
- Age-adjusted rates per 100,000, 5-year age bands consistently present across all years; 2017 excluded (wash-in).

Methods

- Data & cohorting. CDC WONDER, underlying-cause deaths: DLBCL C83.3; comparators PTCL C84, MCL C83.1, FL C82; 1999–2023; 5-year age bands present in all years; 2017 excluded (wash-in).
- Exposure timeline. DLBCL: 2017 (axi-cel), 2018 (tisa-cel), 2021 (liso-cel), 2L expansions 2022. MCL: 2020 (brexu-cel), 2024 (liso-cel). FL: 2021/2022/2024 (axi-cel/tisa-cel/liso-cel; accelerated). PTCL: no FDA-approved CAR-T.
- DiD design. Two-way FE panels: DLBCL vs PTCL; DLBCL vs MCL+FL (pooled). Model: Rate ~ Treat×Post + Year FE + AgeGrp FE + Disease FE; Post=2018–2023; Treat=DLBCL; HC3 SEs clustered by age band.
- Event-study. Reference 2016; dynamic Treat×Year inspected for pre-trends.
- Counterfactual (age-specific). Train 1999–2016 → forecast 2018–2023 (Prophet/NeuralProphet, safe fallbacks) → O–E gaps (/100k).
- Sensitivity. Placebo Post=2012; exclude 2020–2021.

Results

- Main DiD (two-way FE; clustered HC3 by age band).

Post-2018 additional decline in DLBCL mortality relative to controls (per 100,000):

- vs PTCL: +1.32 (95% CI +0.24 to +2.40; p=0.016).
- vs MCL+FL: +1.61 (95% CI +0.44 to +2.78; p=0.0068).

(Note: "Additional decline" is reported as positive; it equals −β from the regression table.)

Comparison	Additional decline (per 100k)	95% CI	p-value
DLBCL vs PTCL	+1.32	+0.24 to +2.40	0.0161
DLBCL vs MCL+FL	+1.61	+0.44 to +2.78	0.00682

Table 1. Key DiD estimates (two-way FE; HC3 age-cluster)

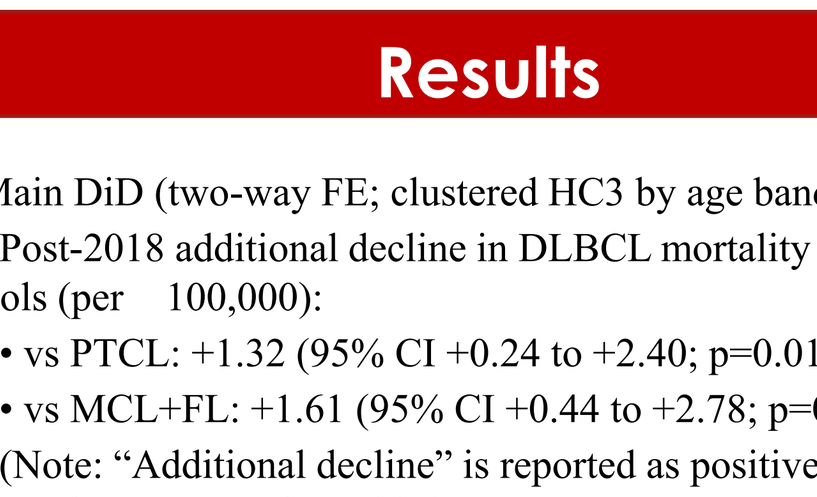


Fig 1. Event-study (base = 2016) for DLBCL vs PTCL; 95% cluster-robust CIs. Pre-trends ~0; post-2018 shifts indicate a DLBCL-specific decline.

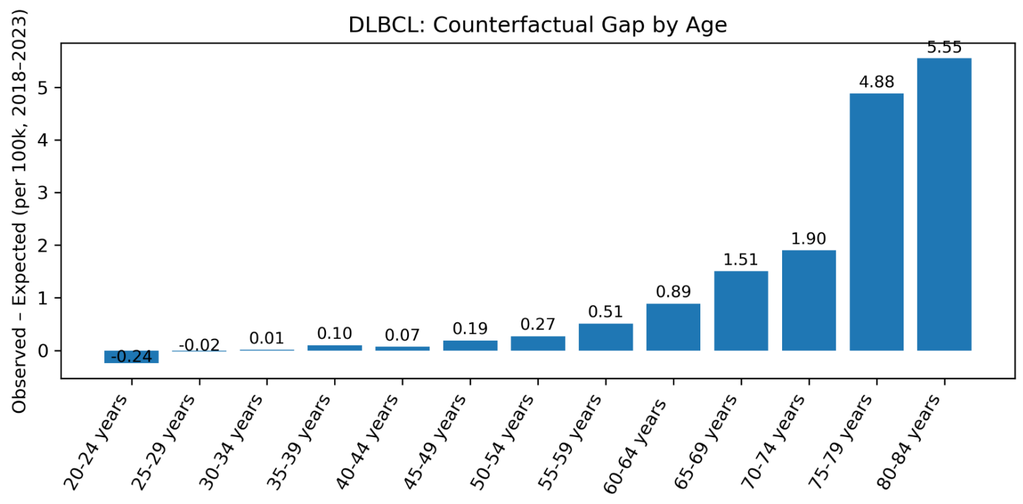


Fig 2. O–E DLBCL mortality by age (2018–2023). Expected from 1999–2016 forecasts; sign shows direction vs counterfactual.

- Event study (ref=2016): Pre-2018 interactions hover around zero; coefficients shift away from zero after 2018, consistent with a disease-specific effect (Fig. 1).
- Age-specific counterfactual gaps (Observed–Expected, 2018–2023):~0 for <55 y; small positive gaps through 55–69 y; increasing positive gaps at ≥70 y with the largest excess in ≥75 y (Fig. 2).
- Controls: PTCL shows no significant post-2018 change; MCL/FL display small, inconsistent shifts—supporting a DLBCL-specific effect.
- Sensitivity: Direction and significance are preserved in a placebo start=2012 and after excluding 2020–2021 (tables).

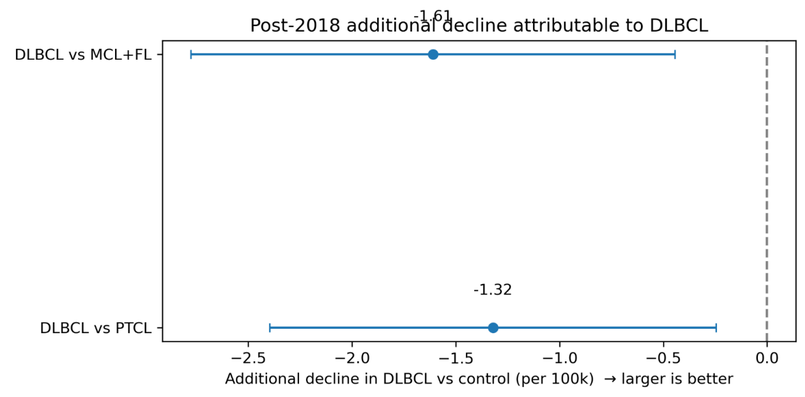


Fig 3. DiD additional decline (= −βTreat×Post) with 95% cluster-robust CIs: +1.32 (PTCL control) and +1.61 (MCL+FL control) per 100k.

Summary

- Nationwide vital-statistics demonstrate a CAR-T–associated, disease-specific, age-dependent reduction in DLBCL mortality that exceeds background trends in other lymphoma subtypes.
- Age-wise counterfactuals are flat <55, while ≥75 y display pandemic-era excess that dilutes population gains.
- Improving access and age-adapted supportive care are needed to extend CAR-T benefits to the oldest adults.

Discussion

- Design strengths: Two-way fixed-effects DiD (Year and Age FEs) with an added Disease FE; inclusion of a negative control (PTCL) and a pooled later-approved comparator (MCL + FL); and an event-study to inspect pre-trends/dynamics.
- Robustness: Effect persists when excluding 2020–2021 (vs PTCL). Main DiD effects remain significant.
- Limitations: Ecological analysis of underlying-cause mortality; lack of patient-level treatment/comorbidity/SES data—unobserved confounding is possible.
- Next steps. Area-level access/uptake analyses; linkage to patient-level datasets for richer adjustment; explicit pre-/post-pandemic splits

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