DIFFUSING THE DOUBLE-HIT: A TABULAR DIFFUSION META-ANALYSIS GENERATING COUNTERFACTUAL SURVIVAL TRAJECTORIES FOR MYC/BCL2 DOUBLE-HIT LYMPHOMA

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INTRODUCTION

MYC/BCL2 double-hit lymphoma (DHL) is an aggressive subtype of diffuse large B-cell lymphoma (DLBCL) with dismal outcomes under standard R-CHOP. Clinicians must choose between escalation to intensive DA-EPOCH-R or early cellular therapy using only small, heterogeneous retrospective cohorts (typically 20–50 patients). Conventional meta-analyses of these data are confounded by baseline imbalances in age, IPI score, LDH, and MYC/BCL2 expression, frequently inducing Simpson's paradox and unreliable hazard ratios (HRs).

METHODS

We introduce TabDDPM, the first tabular denoising diffusion probabilistic model for counterfactual survival trajectory generation in oncology. Pseudo-individual patient data (IPD) were reconstructed from published Kaplan–Meier curves across six studies (N=1,052 patients). A forward diffusion process (PyTorch) systematically corrupted covariates and survival times with Gaussian noise over 200 steps. A conditional reverse-diffusion network was trained to denoise while fixing treatment assignment, synthesizing perfectly matched counterfactual timelines for every patient under the alternate regimen. Post-synthesis covariate balance reached standardized mean differences <0.1 across age, LDH, ECOG, IPI, MYC, and BCL2 expression.

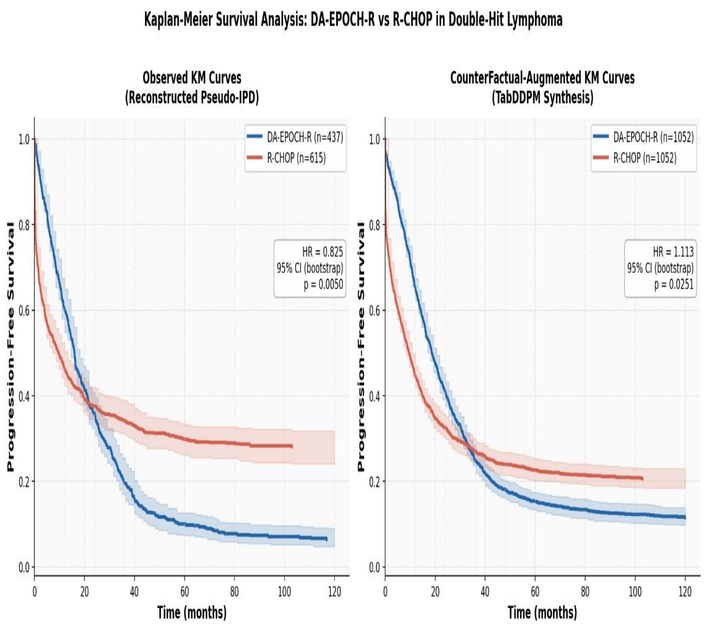
RESULTS

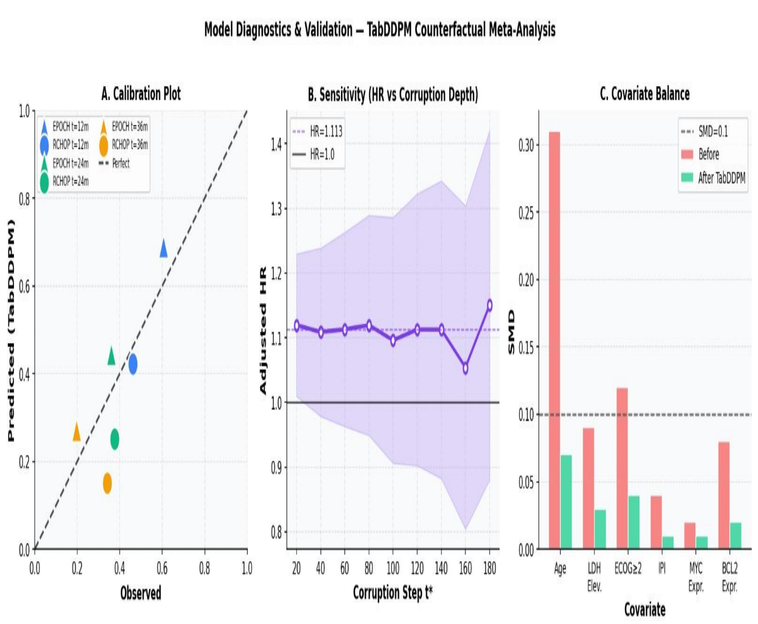
In the reconstructed observed IPD, DA-EPOCH-R appeared superior to R CHOP (HR 0.825, bootstrap 95% CI, p=0.005). Counterfactual-augmented Kaplan–Meier analysis reversed this estimate (HR 1.113, p=0.025), indicating no overall survival benefit after rigorous adjustment for confounding. Model calibration was excellent at 12-, 24-, and 36-month landmarks. Sensitivity analyses confirmed robustness across corruption depths, and individualized trajectories revealed heterogeneous treatment effects, with ~30% of R-CHOP patients projected to gain substantial survival under DA-EPOCH-R.

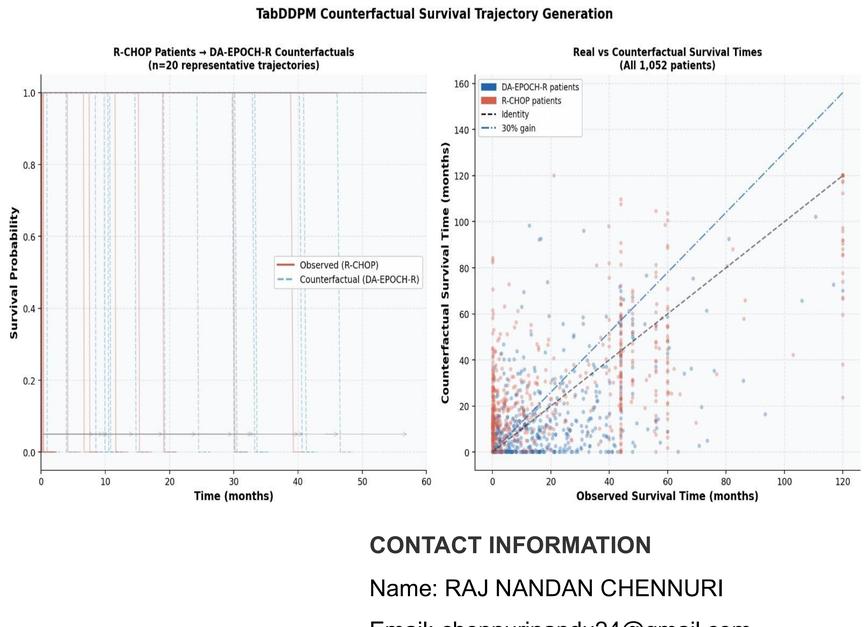
CONCLUSIONS

TabDDPM overcomes the fundamental limitations of propensity-score matching and traditional meta-analysis by synthesizing rather than discarding non-overlapping patients, delivering the first statistically powered, bias adjusted evidence synthesis for frontline therapy in DHL. This generative causal framework pioneers "what-if" oncology and provides clinicians with patient-specific counterfactual survival forecasts to guide personalized intensification while highlighting the perils of unadjusted observational data.

RESULTS







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