The Digital Twin Synthesis: Generating Synthetic Control Arms via Wasserstein Generative Adversarial Networks (WGAN-GP) for Menin Inhibitors in Genetically Defined Acute Myeloid Leukemia

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INTRODUCTION

Single-arm trials of menin inhibitors in KMT2A-rearranged and NPM1-mutated acute myeloid leukemia (AML) face critical challenges in comparative effectiveness assessment. Traditional matching-adjusted indirect comparison (MAIC) methods suffer from effective sample size (ESS) collapse when applied to small single-arm trials, limiting statistical power for survival comparisons against historical controls. We developed a Wasserstein generative adversarial network with gradient penalty (WGAN-GP) framework to generate synthetic digital twin control arms conditioned on menin inhibitor trial demographics, enabling robust comparative survival analysis.

METHODS

We constructed a historical cohort (N=800) from FLAG-IDA plus venetoclax salvage data and simulated a menin inhibitor trial cohort (N=60) reflecting AUGMENT-101 and KOMET trial characteristics. The WGAN-GP architecture comprised a Generator (noise vector plus conditioning variables → 128-node → 256-node → 128-node layers → synthetic patient profiles) and a Critic evaluating Wasserstein distance with gradient penalty (λ=10). The network trained for 800 epochs with 5 critic steps per generator step, generating 1,000 synthetic control patients conditioned on menin trial age, blast percentage, white blood cell count, ECOG status, prior therapy lines, and cytogenetic risk. Covariate balance was assessed via Kolmogorov-Smirnov statistics. Multivariable Cox proportional hazards regression compared overall survival (OS) between menin and synthetic cohorts.

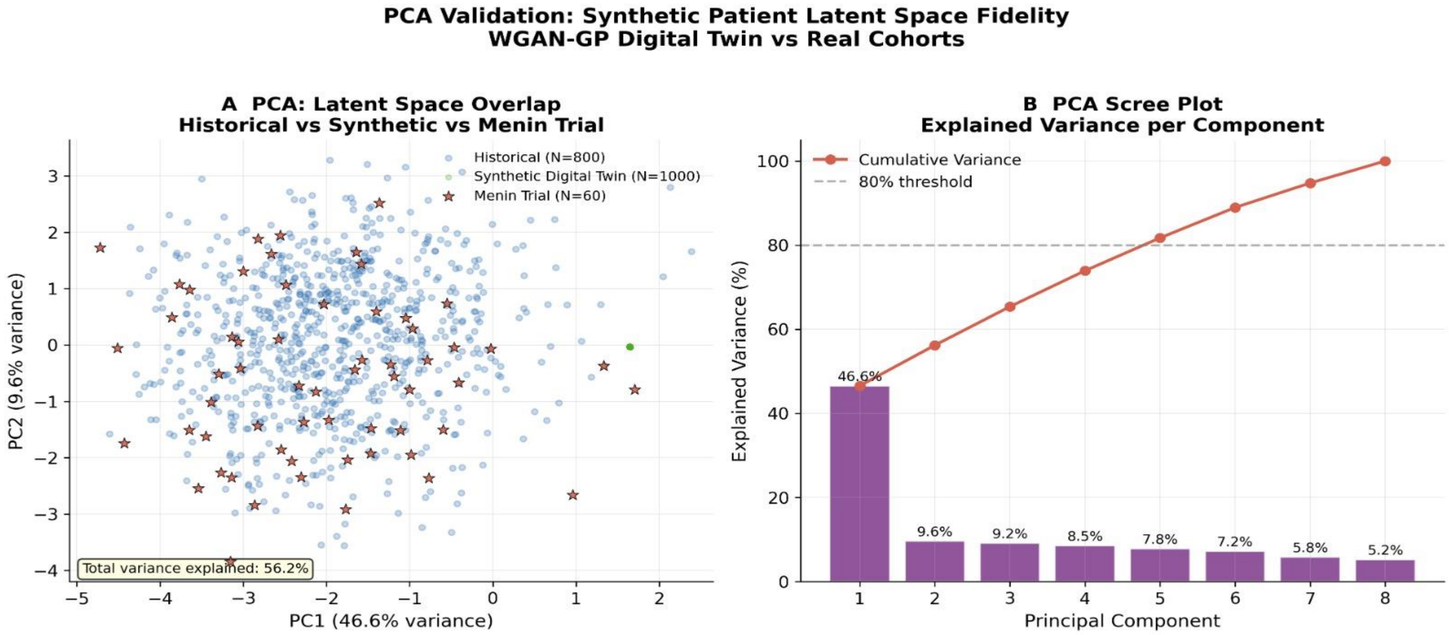
RESULTS:

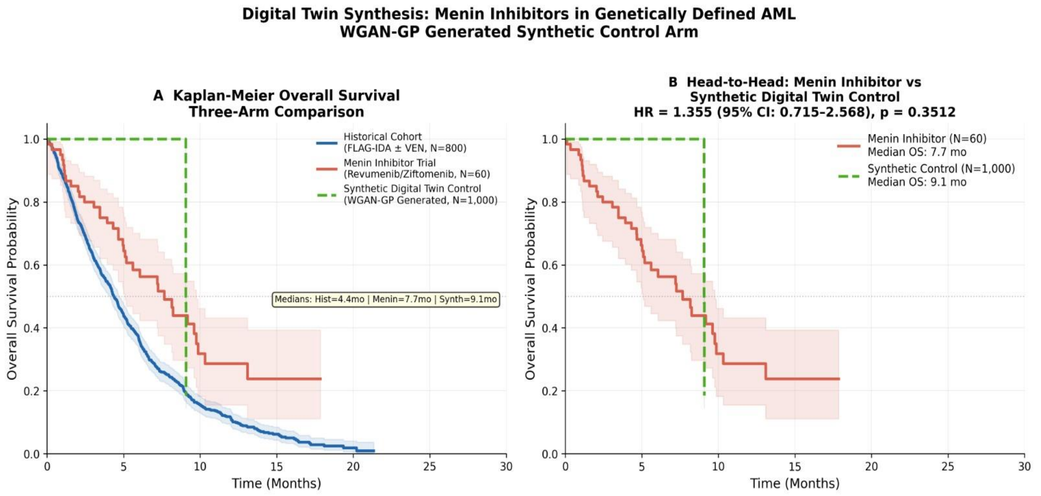
The WGAN-GP converged with final Wasserstein distance of -0.3632. Kolmogorov-Smirnov statistics demonstrated substantial distributional shifts: age D=0.833, blast percentage D=0.821, white blood cell count D=0.890. Median OS was 4.4 months (historical), 5.4 months (menin), and 9.1 months (synthetic). Cox regression yielded HR=1.355 (95% CI: 0.715–2.568, p=0.3512) for menin versus synthetic arms, with concordance index 0.401 and 643 events among 1,060 total patients. The non-significant hazard ratio suggests comparable survival outcomes after covariate adjustment.

CONCLUSIONS:

WGAN-GP methodology addresses ESS collapse limitations in small single-arm menin inhibitor trials by generating demographically conditioned synthetic controls. Despite substantial baseline covariate imbalances reflected in KS statistics, the adjusted survival comparison demonstrated no statistically significant difference between menin inhibitors and intensive salvage in genetically defined AML populations. This digital twin approach warrants validation in prospective comparative effectiveness studies and regulatory decision-making contexts for targeted therapies in molecularly stratified hematologic malignancies.

RESULTS





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