Incorporating Patient's Characteristics in Cancer Phase I Clinical Trials Using Time to DLT: Escalation with Overdose Control (EWOC)

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Phase I cancer clinical trial designs

- Goals of phase I cancer clinical trial:
  - Estimate the maximum tolerated dose (MTD).
  - Assumption: both efficacy and toxicity increase with dose.
  - Minimize overdose rate; maximize effective dose coverage
- Designs:
  - Rule-based approaches: 3+3 and its modifications
  - Model-based approaches: CRM, EWOC, and their extensions.
- EWOC-PH:
  - Time to DLT
  - Proportional Hazards model
  - Late onset toxicity; shorten trial duration

Incorporating Patient's characteristics

- A key assumption by the definition about phase I clinical trial designs
  - patient population is homogeneous in susceptibility to treatment.
  - Individualized MTD can prevent patients being overdosed or being treated under an ineffective dose.
- Model-based approaches:
  - Flexible to incorporate covariates in a Bayesian model
- Aims of this study:
  - Extend EWOC-PH to account for patient's heterogeneity
  - Simulation study was conducted to investigate its operating characteristics.

Model setting

- Let T_j be the random variables representing time to DLT up to time τ, and let $\Omega_n = \{(Y_j, x_j, z_j, \delta_j); j = 1,2,\ldots, n\}$ be the observed data, where $Y_j = \min(T_j, \tau)$, $\delta_j = I(T_j \le \tau)$, and x_j is the dose assigned to patient j, and z_j is the value of covariate for patient j.

- The dose-toxicity relationship is described by the proportional hazards model (Cox, 1972)

$$h(T_j \mid x_j, z_j) = h_0(T_j; \lambda')\exp(\beta \cdot (x_j - x_0) + \eta z_j), \quad \beta > 0$$

- Assuming the baseline hazard is exponential distribution.

$$h(T_j \mid x_j, z_j) = b \cdot \exp(\beta \cdot (x_j - x_0) + \eta z_j), \quad \beta > 0$$

$$L(b, \beta, \eta \mid \Omega_n) = \prod_{j=1}^{n} (b \cdot \exp(\beta(x_j - x_0) + \eta z_j))^{\delta_j} \exp(-Y_j \cdot b \cdot \exp(\beta(x_j - x_0) + \eta z_j))$$

RE-PARAMETERIZATION

- Suppose we have a dichotomized covariate z takes value of 0 and 1 that leads to personalized MTDs: γ_0 if $z = 0$ or γ_1 if $z = 1$

- Define:

$$\Pr(Y \le \tau \mid x = \gamma_i, z = i) = 1 - S(Y \mid \gamma_i, z = i) = \theta, \quad i = 0,1$$
$$\Pr(Y \le \tau \mid x = x_0, z = 0) = 1 - S(Y \mid x_0, z = 0) = \rho_0$$

- Based on the one to one correspondence between Survival function and hazard function

$$b = -\frac{1}{\tau}\log(1-\rho_0); \quad \beta = \frac{1}{\gamma_0 - x_0}\log\left\{\frac{\log(1-\theta)}{\log(1-\rho_0)}\right\}; \quad \eta = \frac{\gamma_0 - \gamma_1}{\gamma_0 - x_0}\log\left\{\frac{\log(1-\theta)}{\log(1-\rho_0)}\right\}$$

- The likelihood function is re-parameterized in terms of γ_0 , γ_1 ,and ρ_0

$$L(b, \beta, \eta \mid \Omega_n) \to L(\gamma_0, \gamma_1, \rho_0 \mid \Omega_n)$$

- Prior distribution/posterior distribution

The design

- The first patient in each group will receive an initial dose of x_0 and be observed until τ. If the patient has DLT before τ , then we would recommend to stop the trial in the subgroup or go with a lower level dose . Otherwise, the next patient is enrolled if available.
- Based on Ω_{j-1}, the j^{th} patient receives the dose so that the posterior probability of exceeding γ_0 if $z_j = 0$ or γ_1 if $z_j = 1$ is equal to a feasibility bound α.
- The feasibility bound α usually starts at $\alpha = 0.25$ and increases in small increments of 0.05 until $\alpha = 0.5$.

Simulation Plan

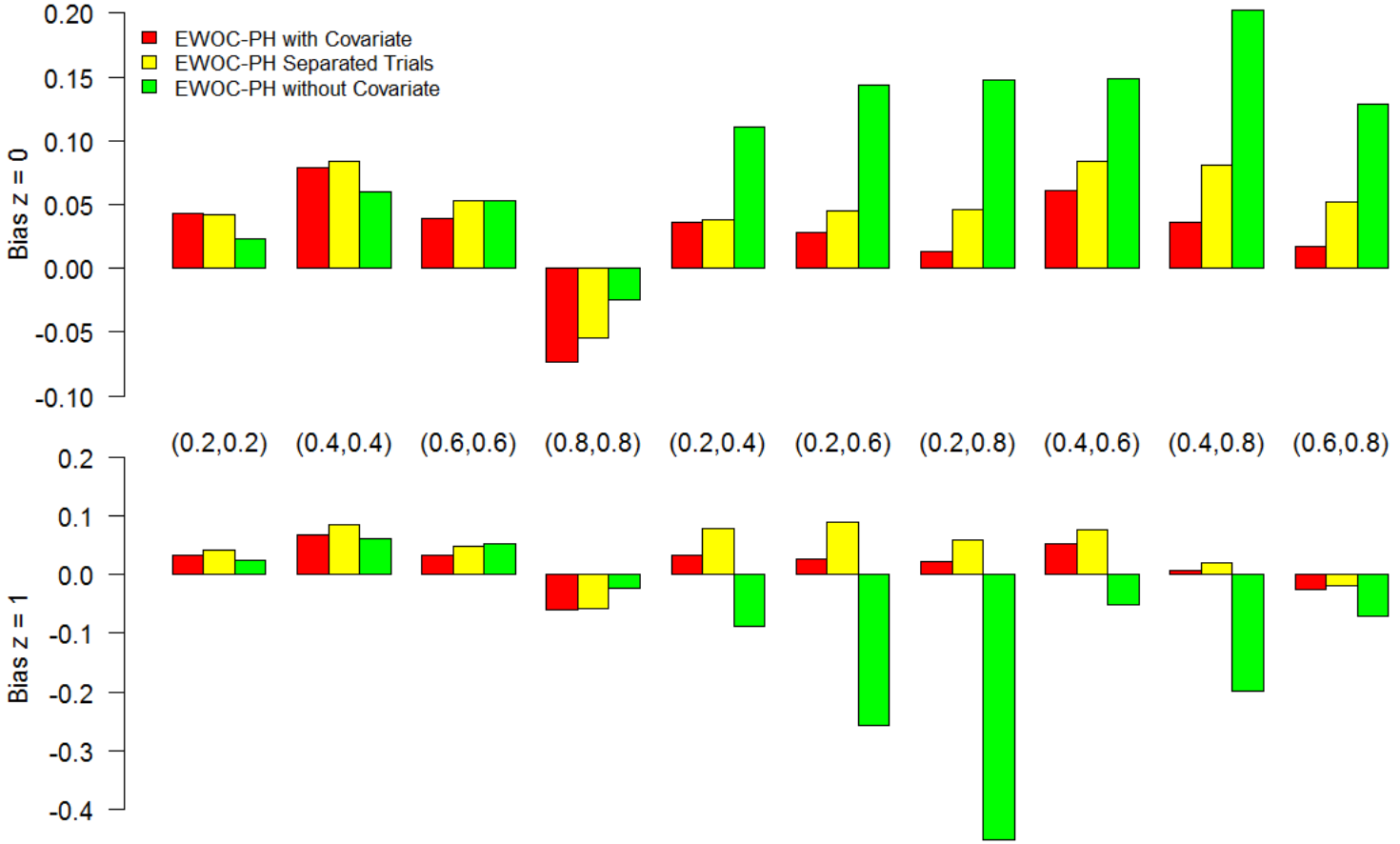
- Compare three models:
  - EWOC-PH with covariate
  - EWOC-PH without covariate
  - Separate trails for each group by EWOC-PH

- Examine the operating characteristics.
  - Bias of estimation
  - Mean Square of Error (MSE) of estimation
  - Probability of DLT
  - Probability of over dose

Simulation parameters

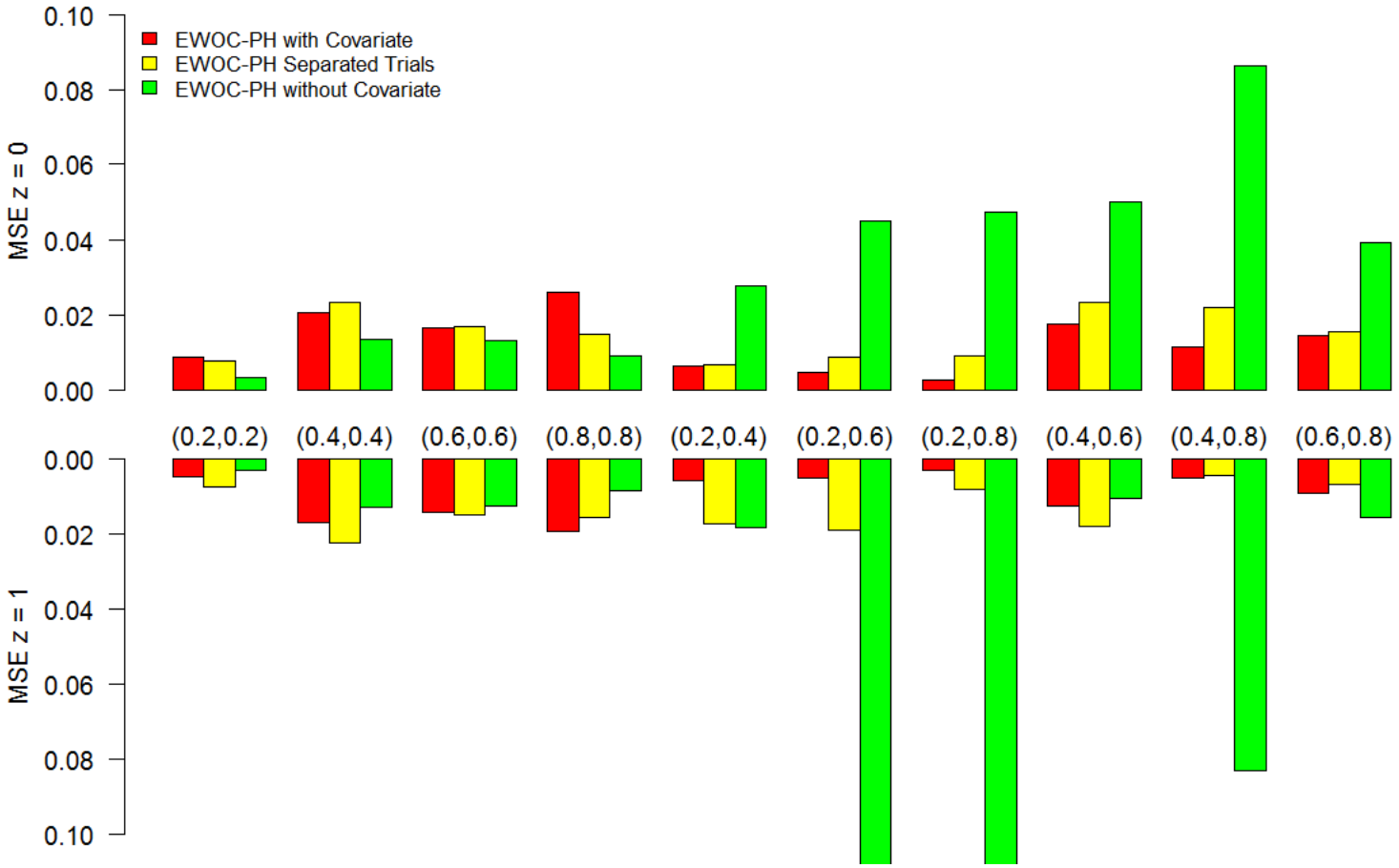
Parameter	Value
N - Sample size	36, 48
α - Feasibility bound	0.25
θ - Target probability of DLT under MTD	0.33
ρ_0 - True probability of DLT at X_0 | z = 0	0.10, 0.05
(γ_0, γ_1) – True MTD combination when z = 0 and z = 1	(0.2, 0.2), (0.4, 0.4), (0.6,0.6), (0.8,0.8), (0.2, 0.4), (0.2, 0.6), (0.2, 0.8), (0.4,0.6), (0.4, 0.8), (0.6, 0.8)
Allocation rate of two groups	1:1, 1:2
Accrual Rate	1, 4
Data generating	$T_j = \frac{-\log(U)}{b \cdot \exp(\beta(x_j - x_0) + \eta z_j)}$

Simulation Results 1
Bias of estimated MTD



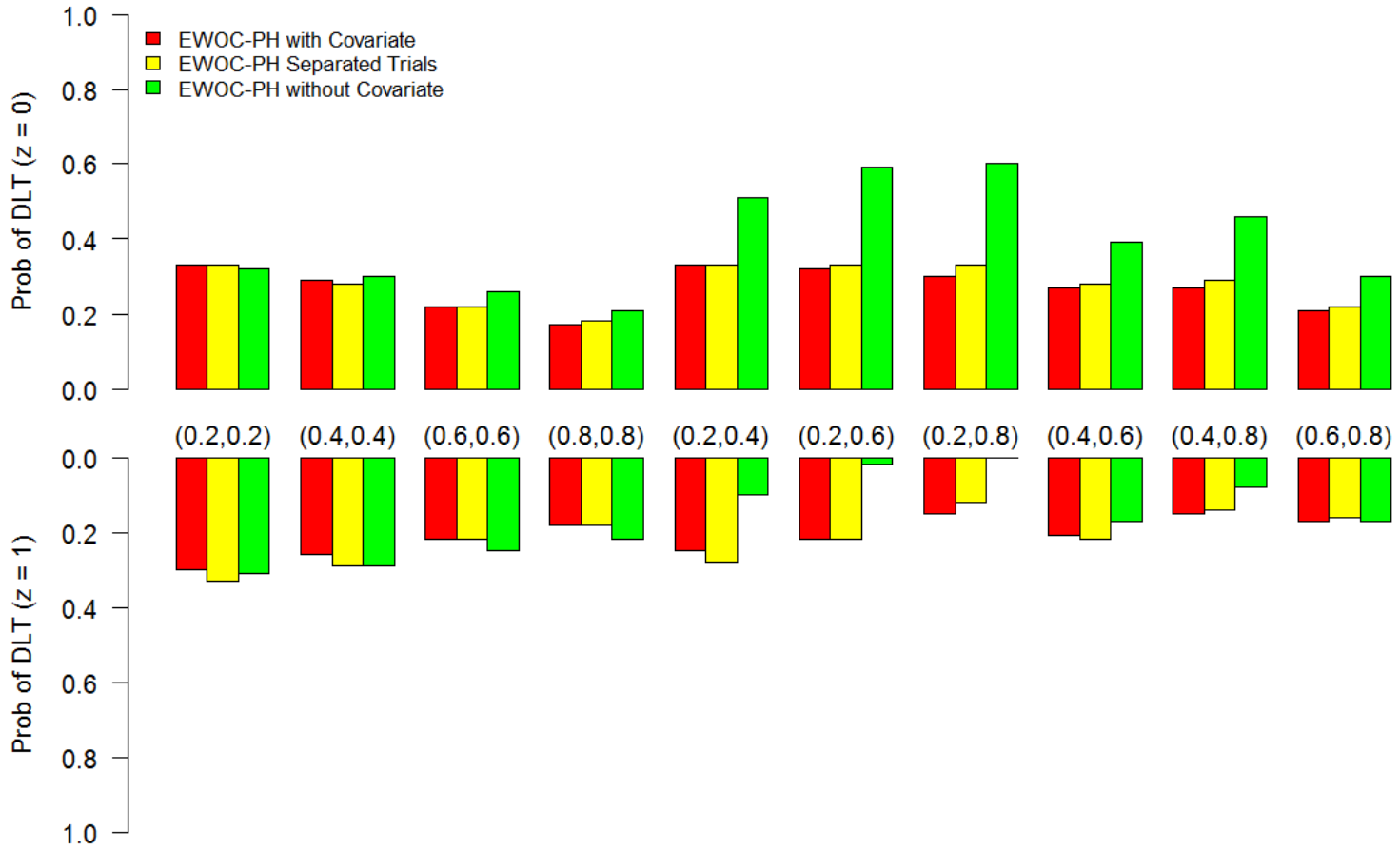
*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at x_0 : $\rho_0 = 0.05$.

Simulation Results 2
MSE of estimated MTD



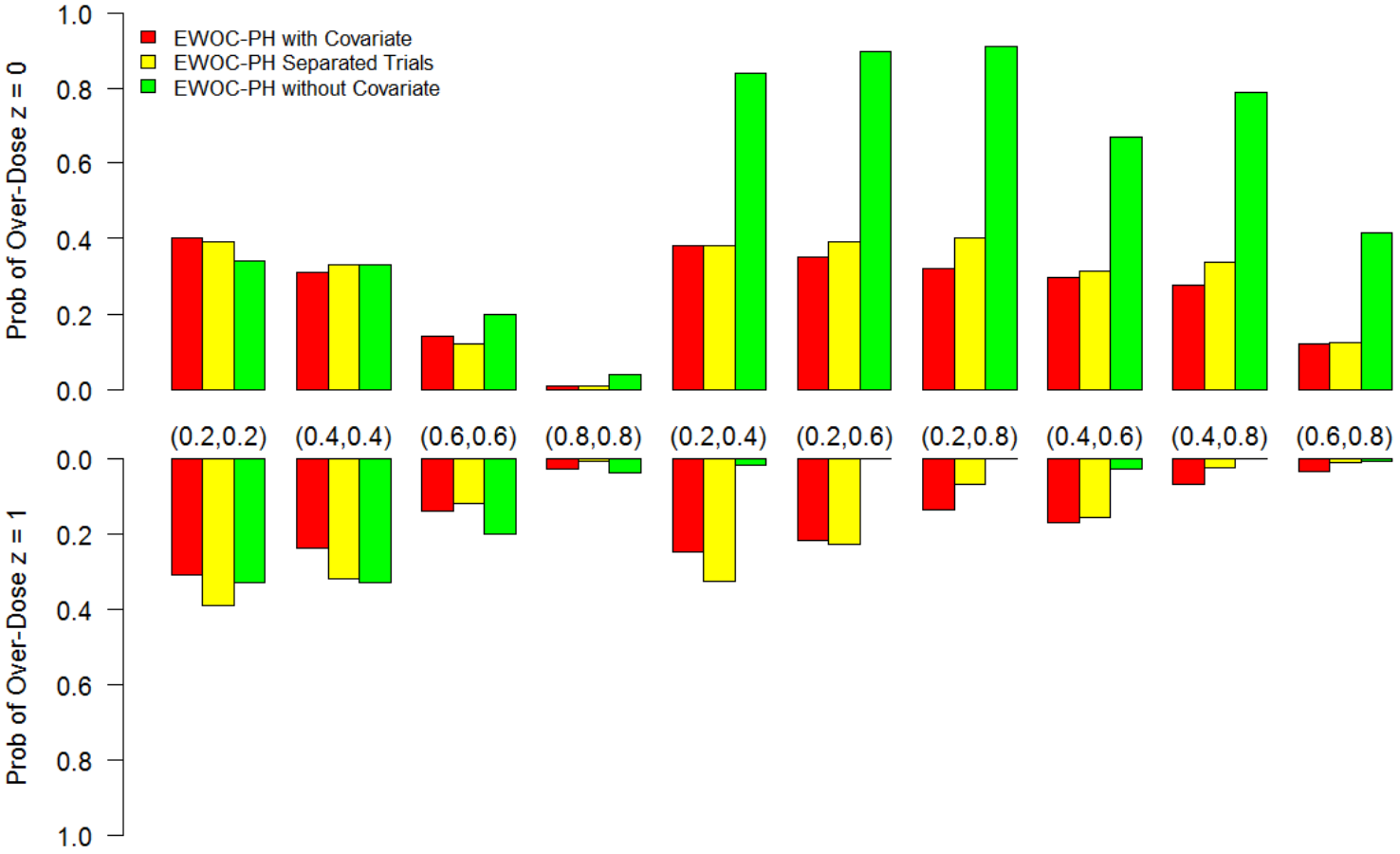
*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at x_0 : $\rho_0 = 0.05$.

Simulation Results 3 Probability of DLT



*selected results summary for sample size = 48, accrual rate = 4, allocation rate = 0.5, and probability of DLT at x_0 : $\rho_0 = 0.05$.

Simulation Results 4
Probability of over-dose



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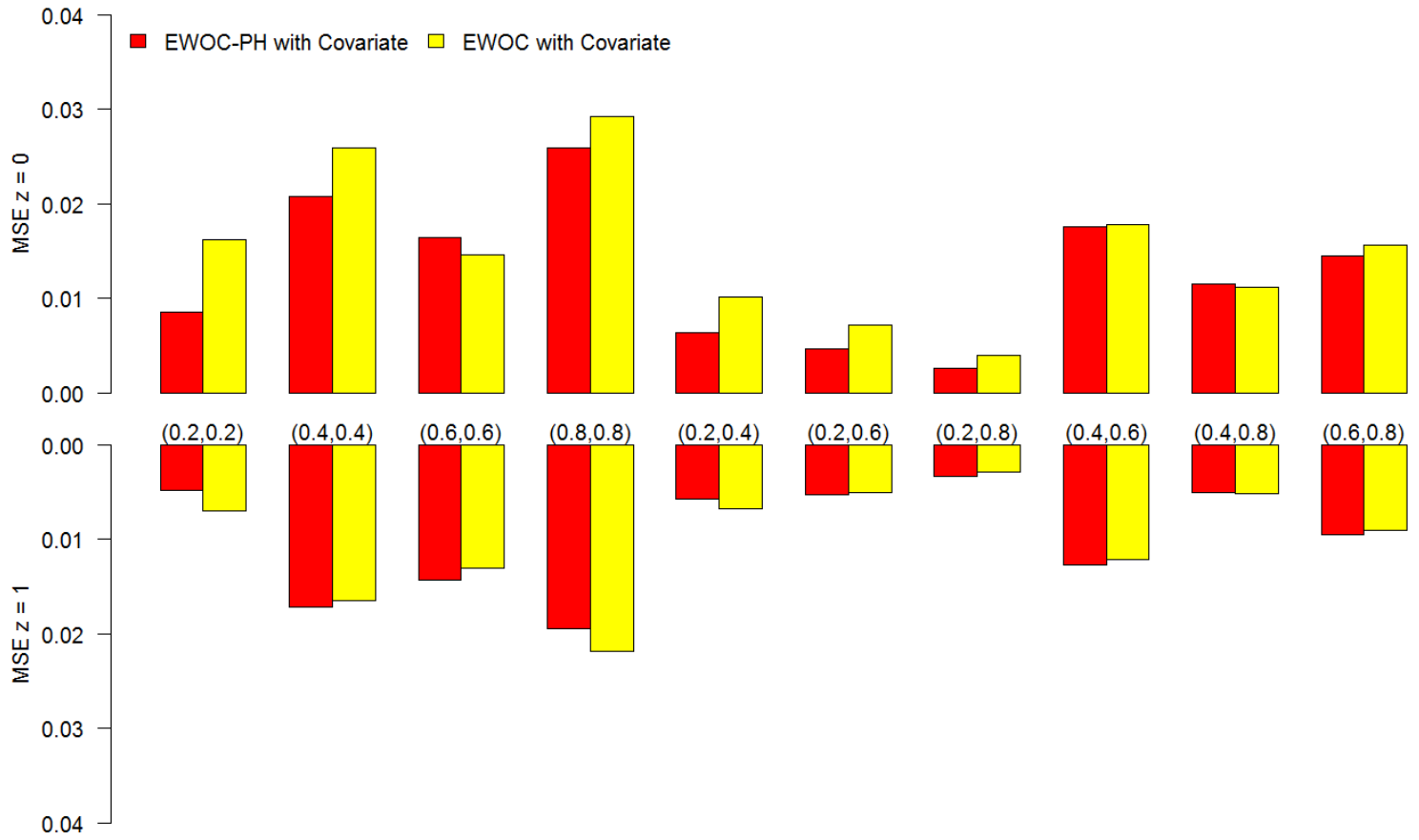
Simulation Results 5
Compare to EWOC with Covariate



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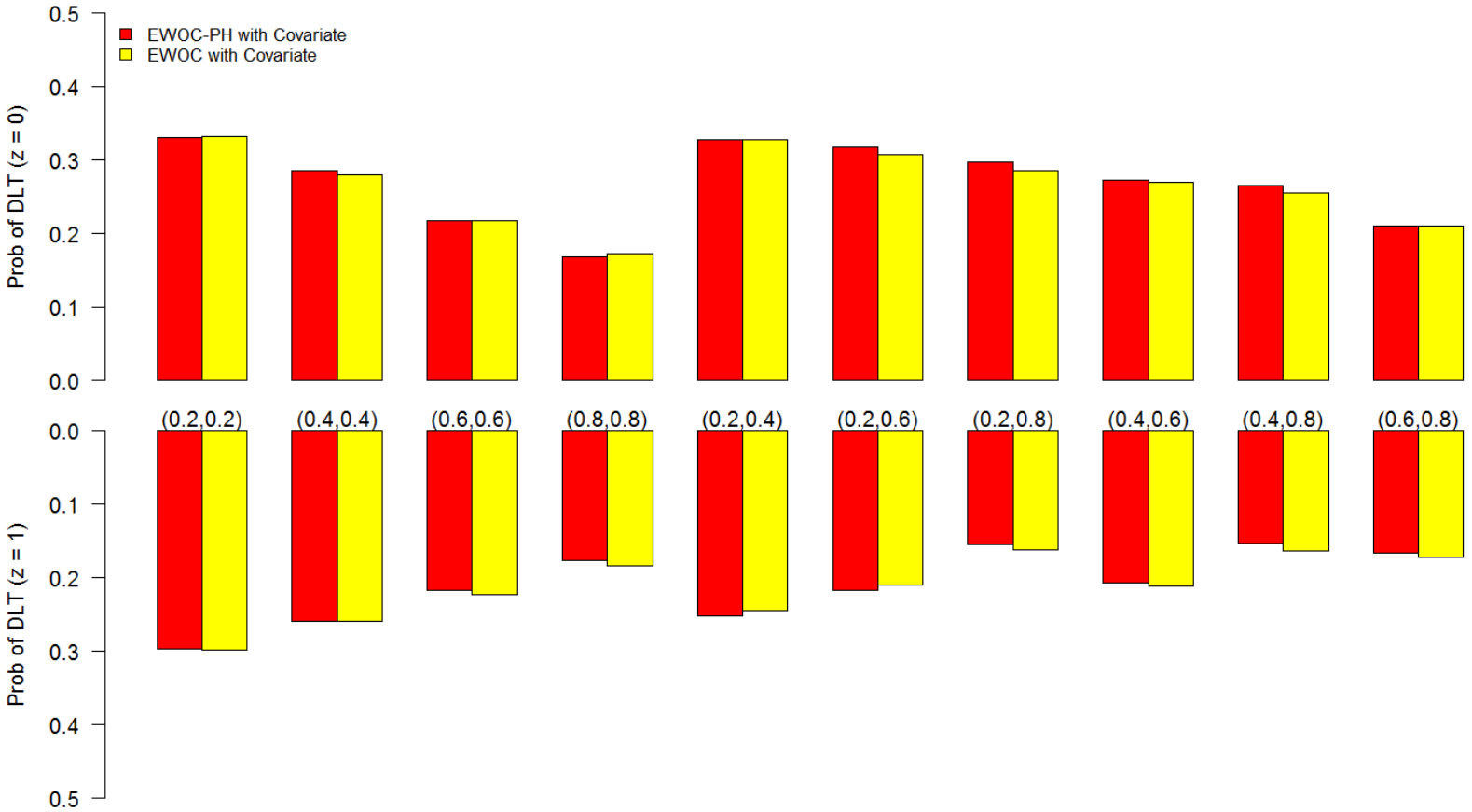
Simulation Results 6
Compare to EWOC with Covariate



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Conclusion

- This study extends EWOC-PH to incorporate patient covariates. The results are similar to those from standard EWOC with covariate with an up to 30% improvement in MSE.
- When comparing to EWOC-PH without covariate design
  - In a heterogeneous patient population, our approach has more than 100% improvement in efficiency (MSE)
  - In a homogeneous patient population, our approach has only an up to 30% decrease in efficiency (MSE).
- Modeling patient heterogeneity in terms of susceptibility to treatment increases the probability that patients will be treated at safer and more efficacious doses, and estimation of personalized MTDs increases the probability that the best treatment plan will be used in subsequent phase II and III clinical trials.

THANK YOU!

QUESTIONS OR COMMENTS?