

Introduction

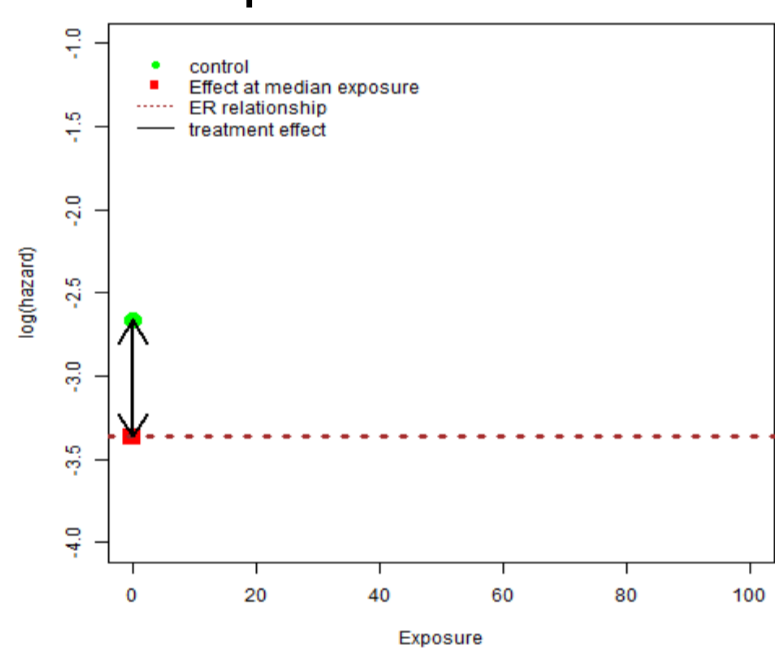
Exposure response (ER) analyses have been commonly used for evaluating the dose used in oncology trial and for regulatory decisions¹. The Cox model which assumes a linear relationship between the log(hazard) and exposure is often used because data are not sufficient to characterize a more complex model. The issue with the model is that a positive ER relationship could be falsely identified if data from both the control (C) and experimental (E) arms are used, and the exposures for patients in arm C are assigned a zero value. Here, the ER relationship could be driven by the efficacy difference between E and C while the true ER relationship is absent. To manage the issue, two other analyses are often conducted: A) when data from the C and E arms are used, a treatment effect in addition to the exposure effect is included in the ER model or, B) data only from E are used in ER analysis. However, the power of detecting the ER relationship may be reduced by both methods A and B. Simulations were conducted to evaluate the false positive rate for the ER relationship, and the power of detecting an ER relationship when data from both arms are included under various effect and sample sizes. The impacts of the methods A and B on the power of detecting ER relationship are also evaluated. In addition, we explored the use of diagnostic plots in evaluating the ER relationship in oncology trials.

Methods

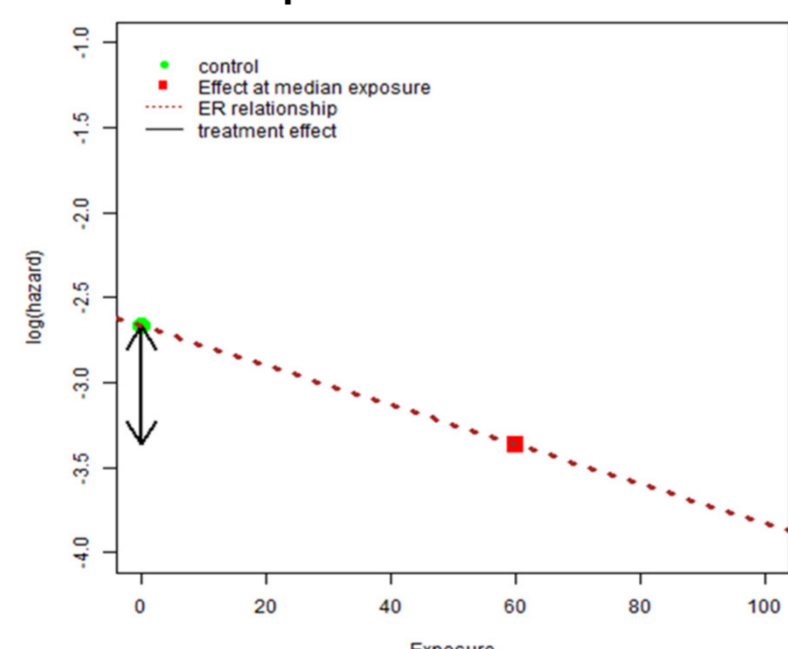
Simulation Scenarios

- An exponential distribution is assumed for event times for patients in arm C with a median survival time of 10 months.
- Exposures are assumed to be a log-normal distribution with a mean of 4 ng/mL and a standard deviation (sd) of 0.4 in log-domain.
- Tested treatment effects: hazard ratio (HR) of 0.5, 0.6, 0.7, and 0.8 between arms E and C.
- Tested exposure effects: HR of 0.995, 0.99, 0.985, 0.98 for 1 unit exposure change which corresponds with a HR of 0.76, 0.56, 0.44, and 0.33 at the median concentration of E to C (HRMC).
- Sample size: 80, 120, 150, 250 patients per arm
- Treatment duration: 40 months. If predicted event time > 40 months, the patient status was censored.
- 1000 trials were simulated.
- Simulation scenarios:

Scenario I: treatment effect is not exposure related



Scenario II: treatment effect is exposure related



Assessments

- Treatment/exposure effect: A cox proportional model was used.

$$\log(\lambda) = \log(\lambda_0) + \beta_1 * \text{Effect}; \quad \text{HR} = \exp(\beta_1)$$

λ : treatment hazard; λ_0 : baseline hazard; Effect: treatment or exposure; β_1 : coefficient for the effect

- Criteria for a positive effect: $p < 0.05$ and estimated HR < 1

$$\text{Power (\%)} = \frac{\# \text{ of positive trials}}{\# \text{ of simulated trials}} * 100$$

$$\text{Bias (\%)} = \frac{\text{true hazard ratio} - \text{estimated hazard ratio}}{\text{true hazard ratio}} * 100$$

- Models used in Method A and B

$$\text{A. } \log(\lambda) = \log(\lambda_0) + \beta_1 * \text{TRT} + \beta_2 * \text{Conc}$$

$$\text{B. } \log(\lambda) = \log(\lambda_0) + \beta_2 * \text{Conc}$$

- Diagnostic plot: Martingale residual vs drug exposure

Software: R (version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Scenario I

- The power of identifying a treatment effect and the rate of identifying a false ER relationship is presented in Figure 1 and 2, respectively.
- The rates of identifying a false ER relationship by Method A are presented in Figure 3. Similar results were observed in Method B (not shown).
- The diagnostic plots from four randomly selected trials when a false ER relationship is identified are presented in Figure 4.
- Diagnostic plots of residuals vs exposure for a model in which no covariate is included are presented in Figure 7.

Scenario II

- The power of identifying an ER relationship is presented in Figure 5.
- The power of identifying an ER relationship by Method A is presented in Figure 6.
- Diagnostic plots of residual vs exposure for a model in which no covariate is included are presented in Figure 8.

Figure 1: The power of detecting a treatment effect

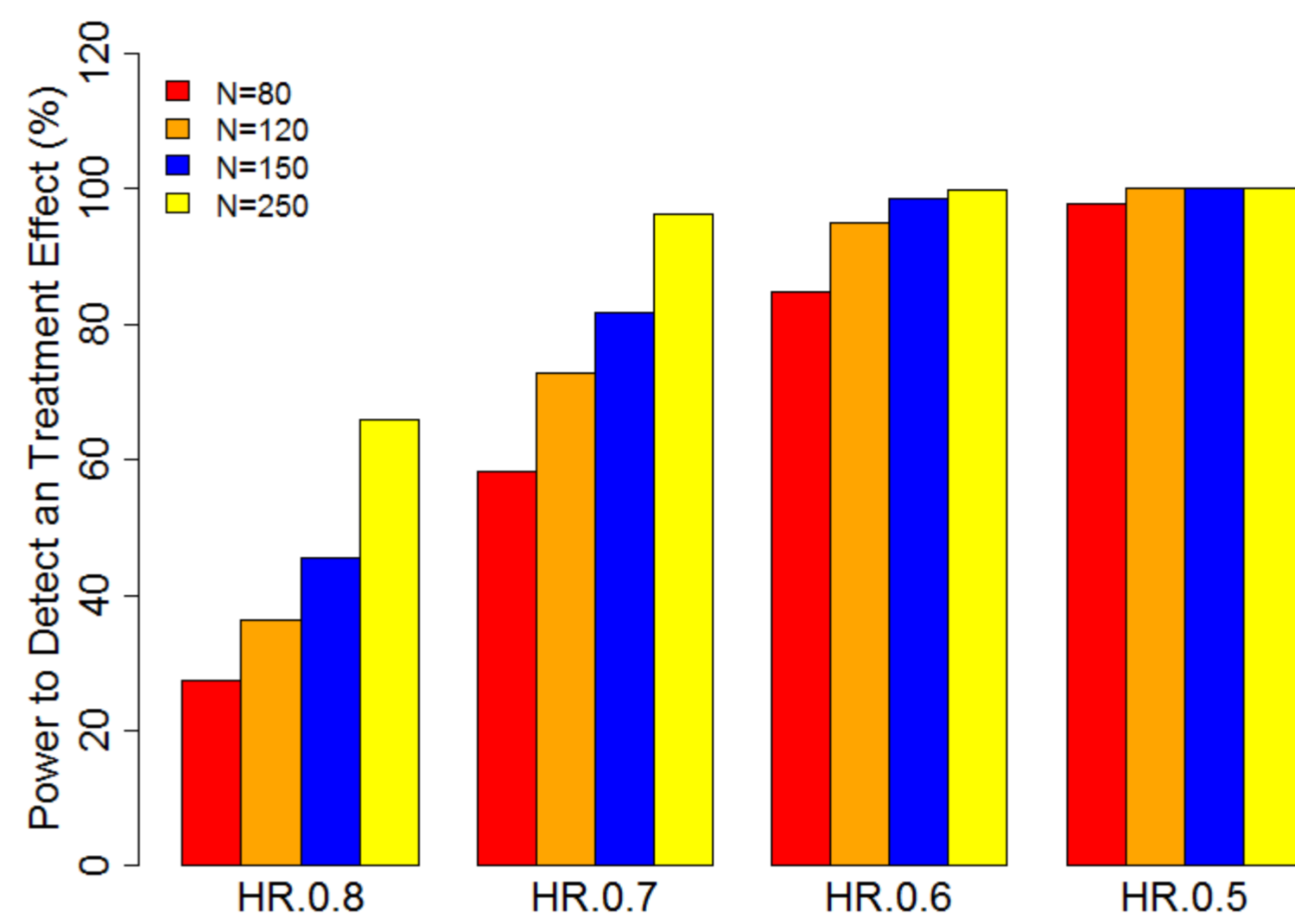


Figure 2: The rate of a false ER relationship

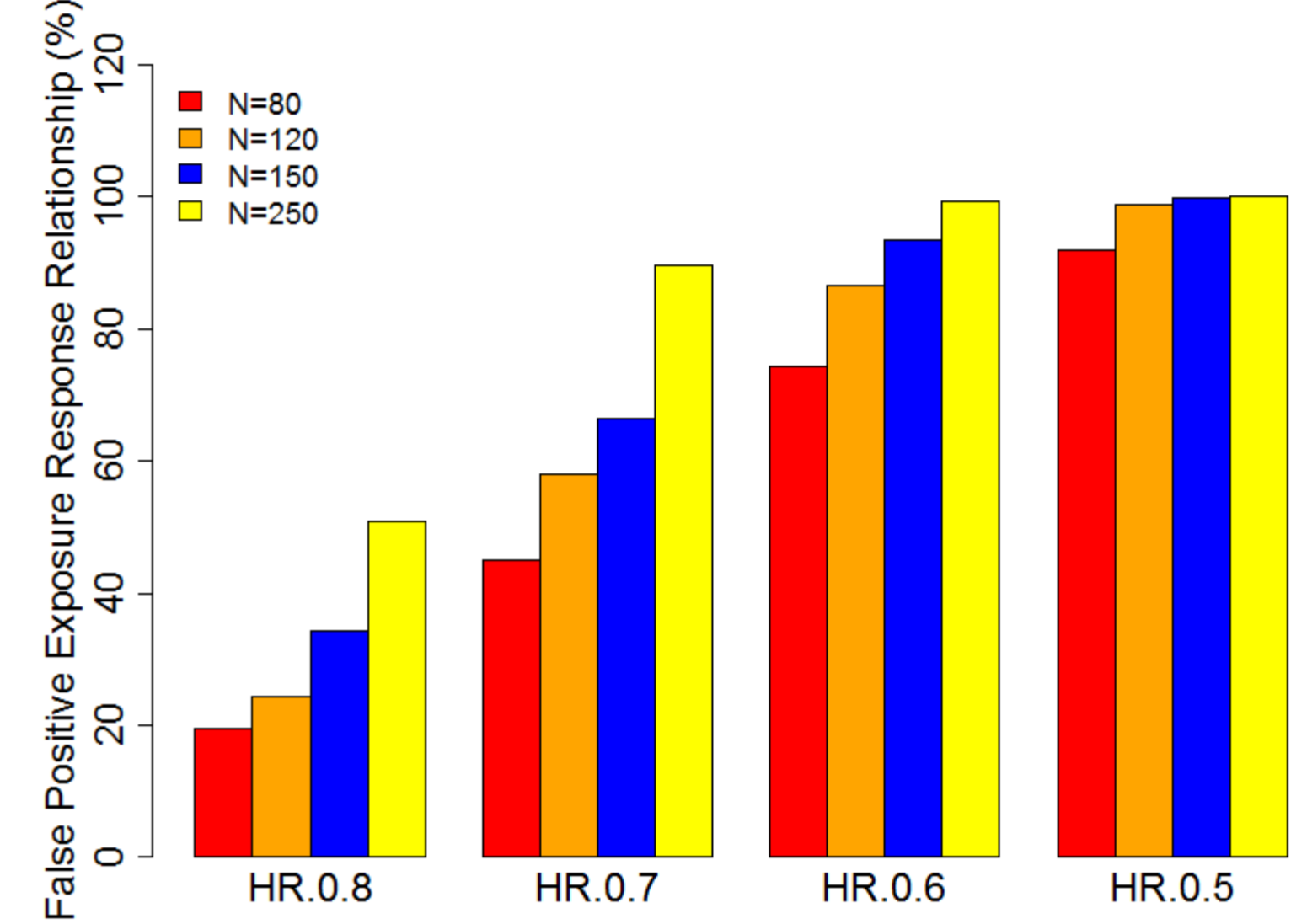


Figure 3: The rate of a false ER relationship by Method A

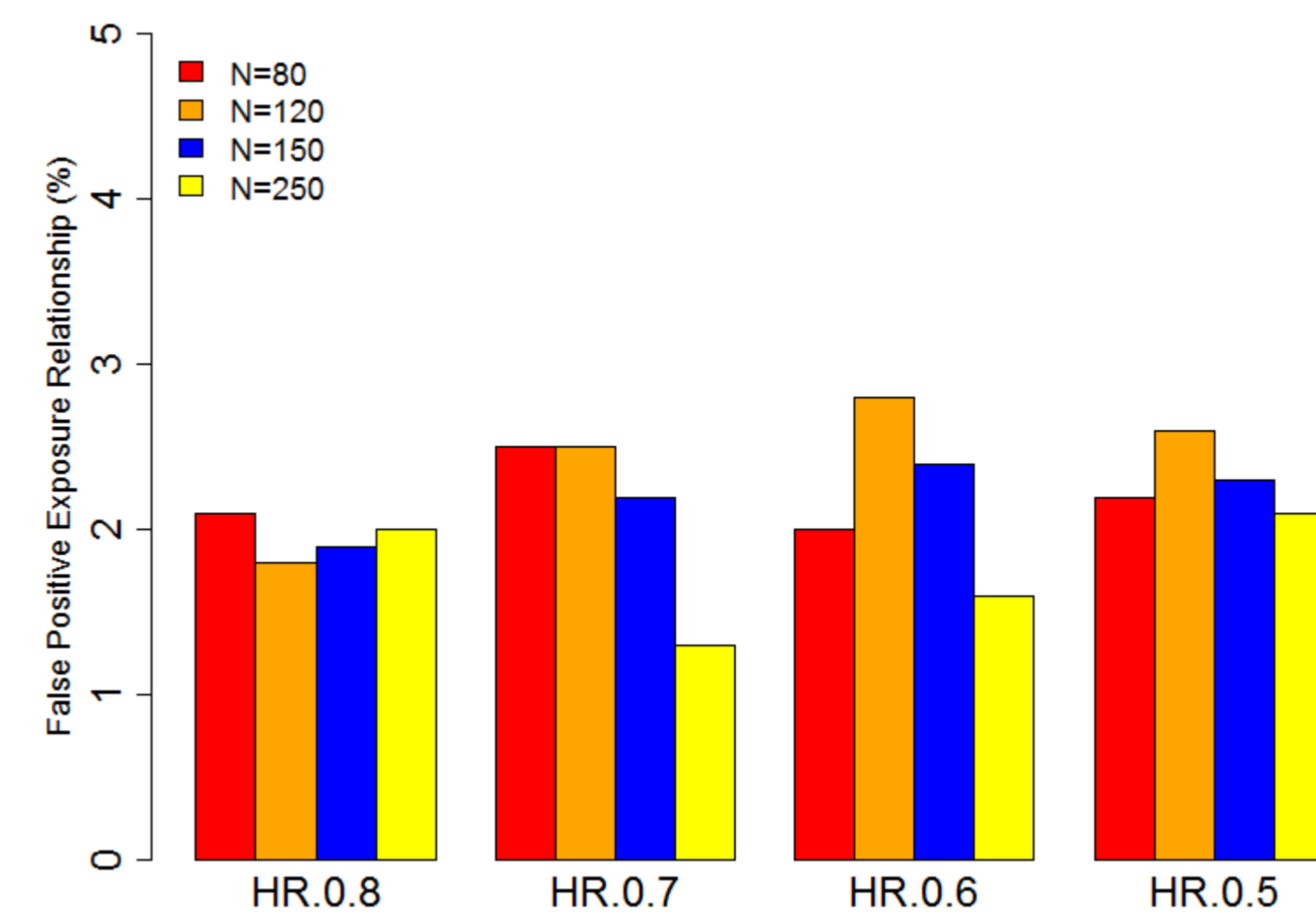


Figure 4: The rate of a false ER relationship by Method A

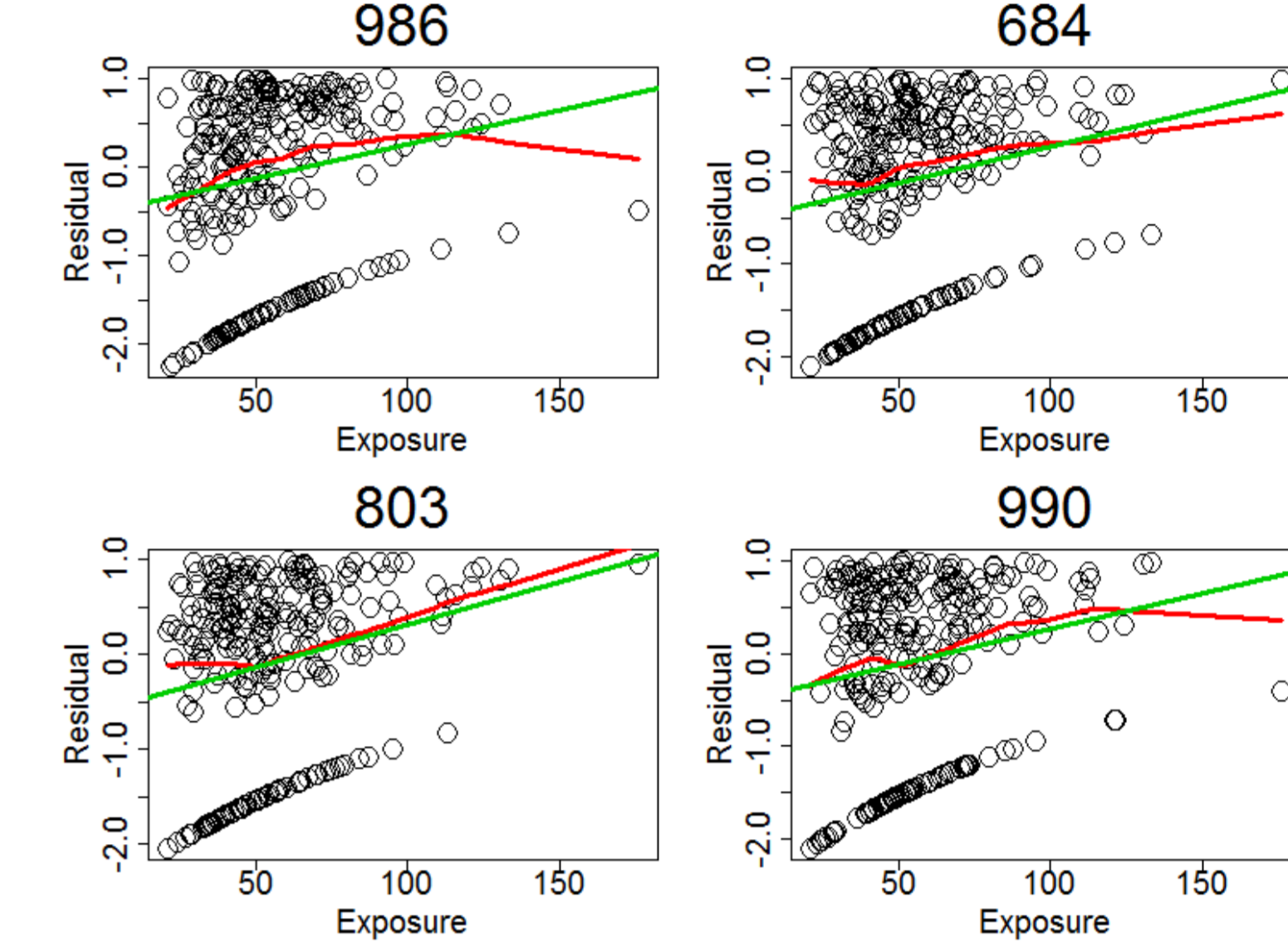


Figure 5: The power of detecting ER relationship

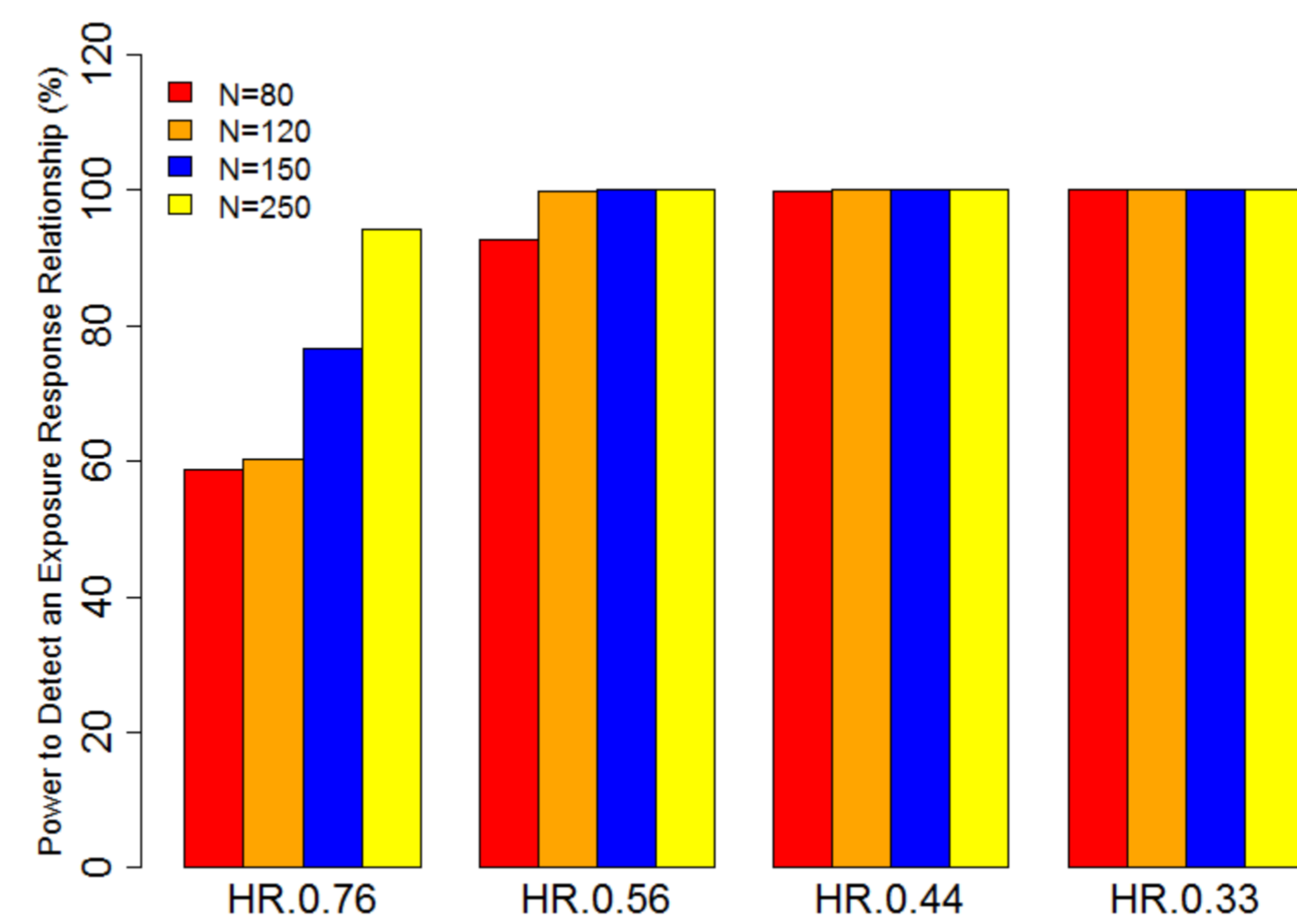


Figure 6: The loss of power of detecting ER relationship using method A

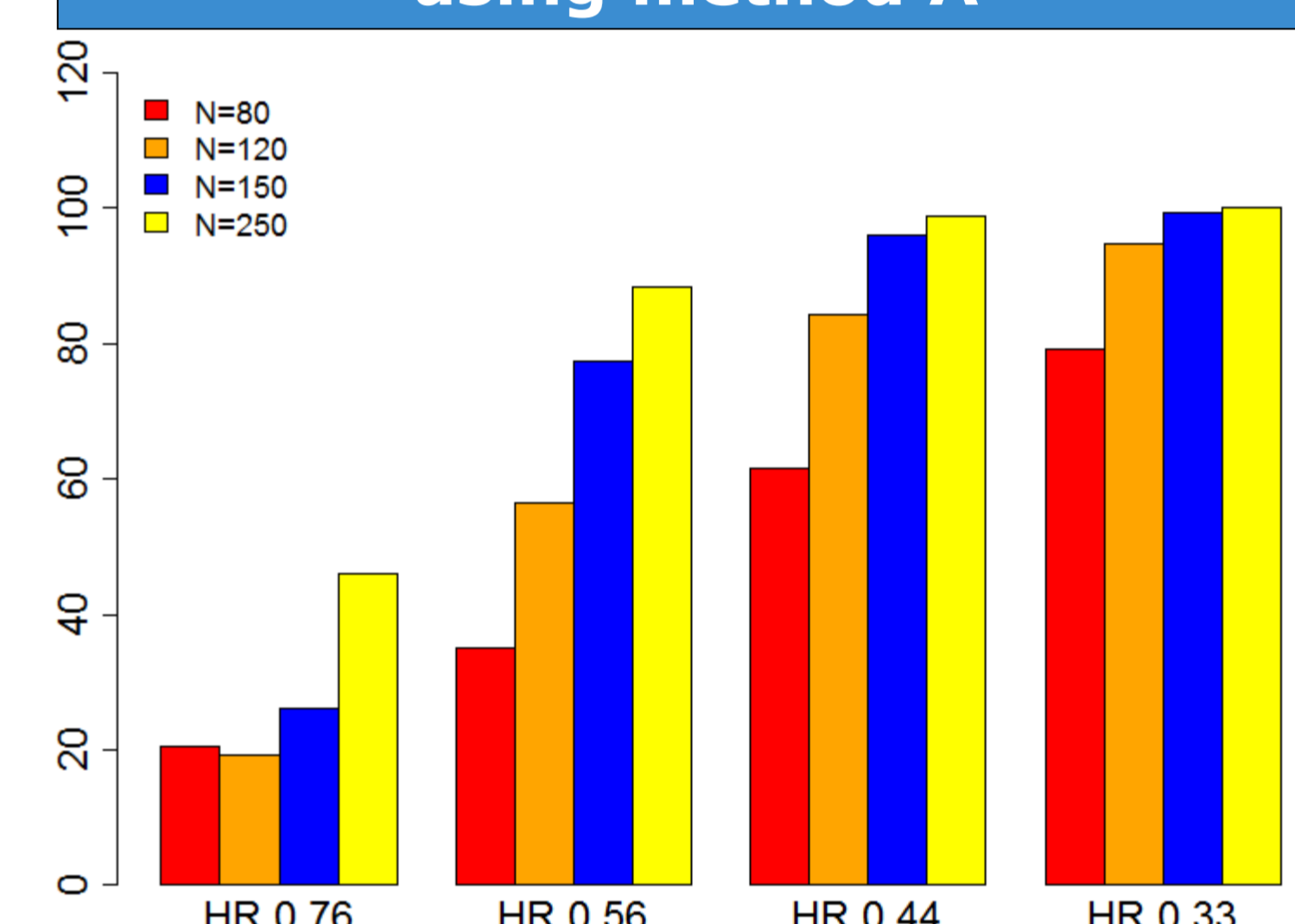


Figure 7: The Diagnostic plots when ER relationship is absent

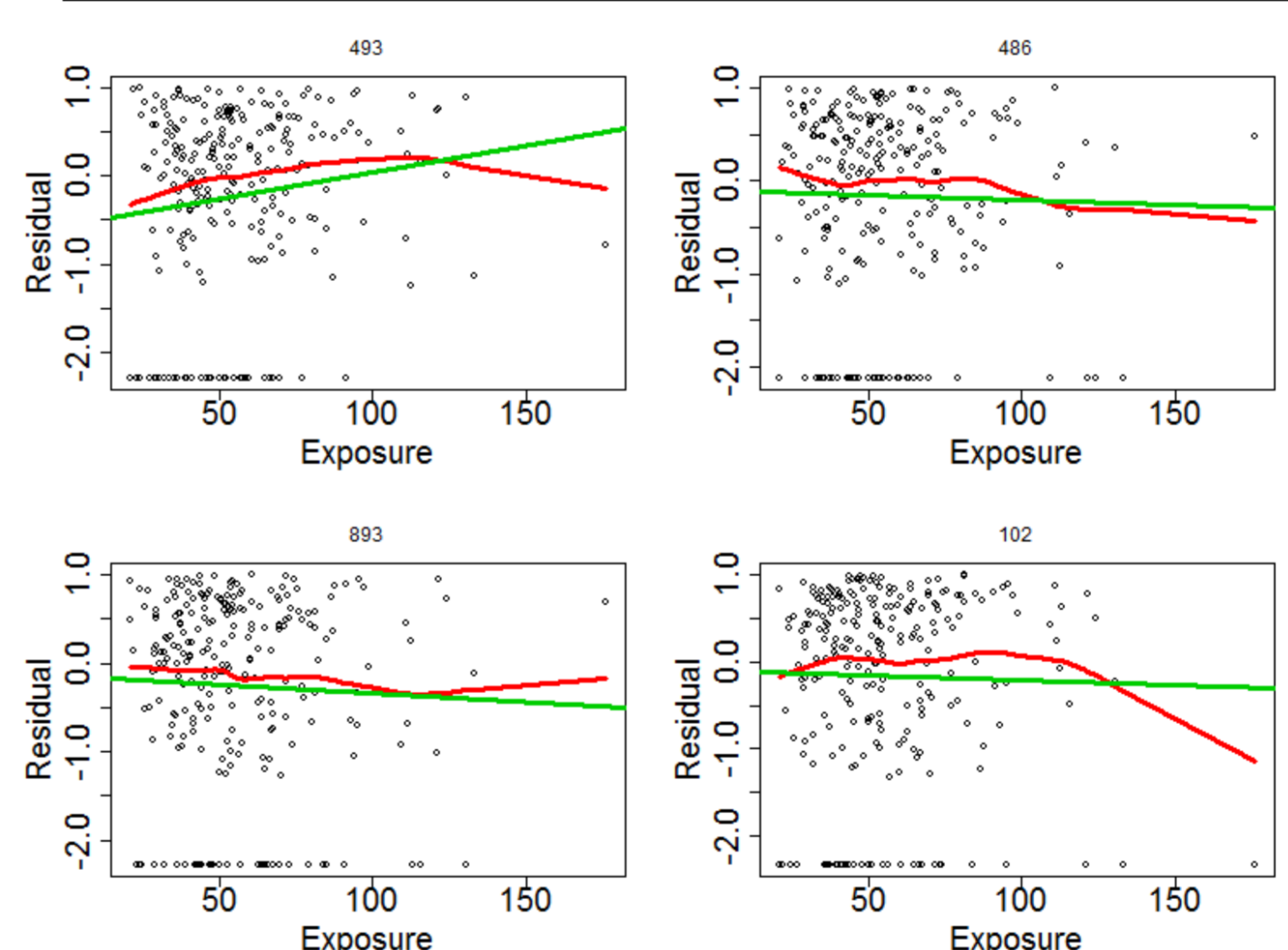
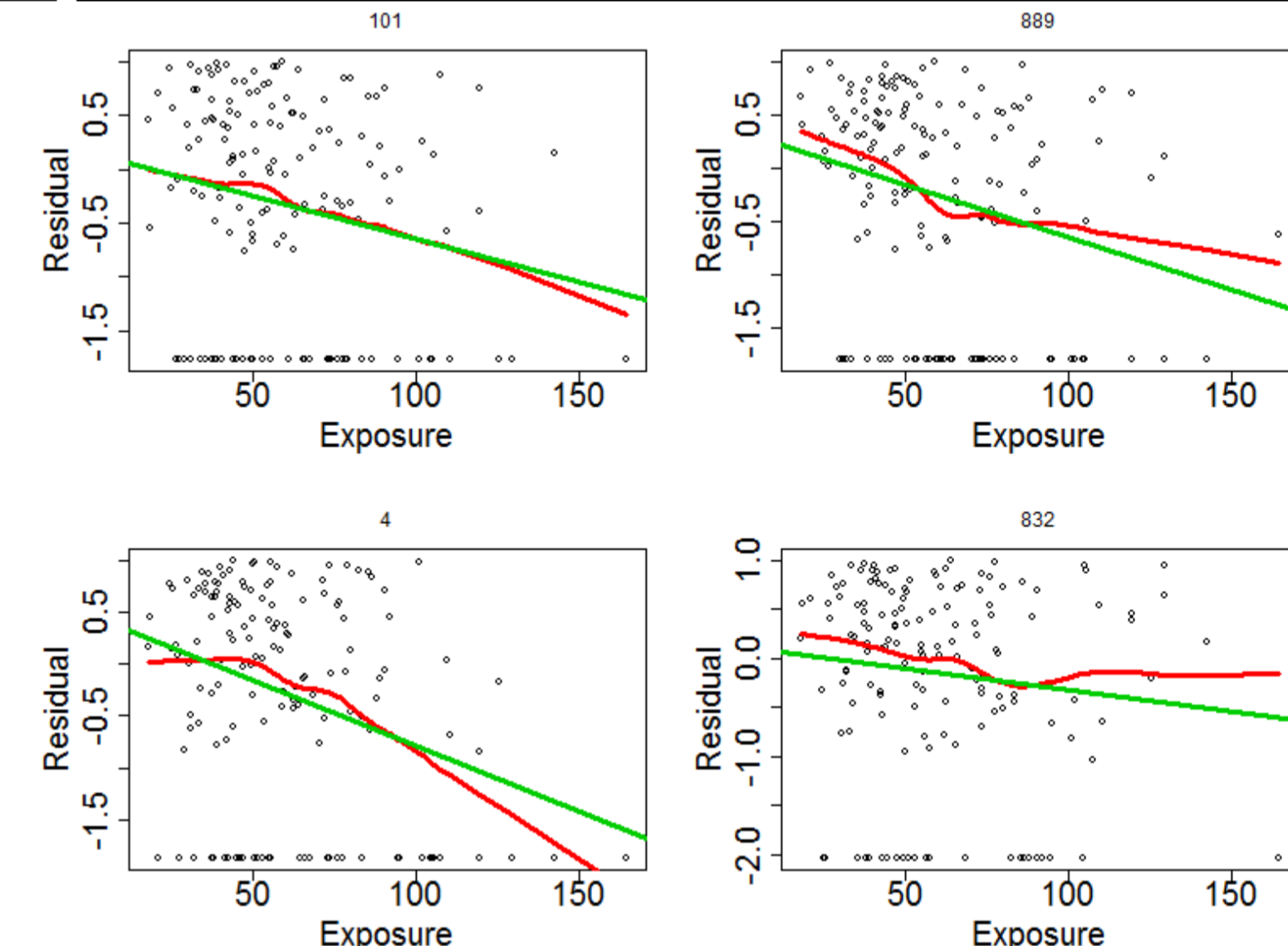


Figure 8: The Diagnostic plots when ER relationship is present



When HRMC were 0.76, 0.56, 0.44, and 0.33, sample size = 250, the bias on the HRMC estimate was -9.5%, -2.8%, -0.6%, and -1.0%, respectively. However, at sample size = 80, the corresponding bias was -30%, -26%, -17%, and -11%, respectively.

Conclusions

- When a Cox model is used to characterize an ER relationship in an oncology trial, the chance of identifying a false ER relationship is high if the exposure values are assigned a zero in patients in the control group.
- When a false ER relationship is identified, an upward trend between the residuals and exposure is observed. Diagnostic plots should be created to examine if the ER relationship is false.
- The rate of a false ER relationship can be significantly reduced if the treatment effect in addition to the exposure effect is included in the model or data only from the control arm are used in ER analysis. However, the power of identifying an ER relationship when present is reduced, particularly when the effect and sample sizes are relatively small.
- The diagnostic plots from a model in which covariates are not included should be created to guide the ER analysis.
- The power to identify an ER relationship from a Phase 2 study, e.g. 80/arm is often limited, but from Phase 3, e.g. 250/arm is reasonable.

References