Supporting Information for "Improving sandwich variance estimation for marginal Cox analysis of cluster randomized trials" by Wang et al.

Web Appendix A

Derivation of the martingale residual-based bias-corrected sandwich variance estimator

We can write the martingale as

$$M_{ij}(t;\boldsymbol{\beta}) = \widehat{M}_{ij}(t;\widehat{\boldsymbol{\beta}}) - \left\{\widehat{M}_{ij}(t;\widehat{\boldsymbol{\beta}}) - \widehat{M}_{ij}(t;\boldsymbol{\beta})\right\} - \left\{\widehat{M}_{ij}(t;\boldsymbol{\beta}) - M_{ij}(t;\boldsymbol{\beta})\right\}, \tag{1}$$

where we define

$$\begin{aligned}\widehat{M}_{ij}(t;\boldsymbol{\beta}) &= N_{ij}(t) - \int_0^t Y_{ij}(u)\widehat{\lambda}_0(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})du \\ &= N_{ij}(t) - \int_0^t Y_{ij}(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})\sum_{k=1}^{n}\sum_{l=1}^{m_k}\frac{dN_{kl}(u)}{S^{(0)}(\boldsymbol{\beta};u)}.\end{aligned}$$

By the first-order Taylor Series expansion, the second term of (1) can be written as

$$-\left\{\widehat{M}_{ij}(t;\widehat{\boldsymbol{\beta}}) - \widehat{M}_{ij}(t;\boldsymbol{\beta})\right\} = \widehat{\boldsymbol{D}}'_{ij}(t;\boldsymbol{\beta}^*)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}),$$

where $\widehat{\boldsymbol{D}}_{ij}(t;\boldsymbol{\beta}^*) = \frac{\partial \widehat{M}_{ij}(t;\boldsymbol{\beta})}{\partial \boldsymbol{\beta}}|_{\boldsymbol{\beta}^*}$, $\boldsymbol{\beta}^*$ is on the line segment joining $\widehat{\boldsymbol{\beta}}$ and $\boldsymbol{\beta}$, and

$$\begin{aligned}\frac{\partial \widehat{M}_{ij}(t;\boldsymbol{\beta})}{\partial \boldsymbol{\beta}} &= \int_0^t Y_{ij}(u)\boldsymbol{Z}_{ij}\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})\sum_{k=1}^{n}\sum_{l=1}^{m_k}\frac{dN_{kl}(u)}{S^{(0)}(\boldsymbol{\beta};u)} \\ &\quad - \int_0^t Y_{ij}(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})\sum_{k=1}^{n}\sum_{l=1}^{m_k}\frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta},u)dN_{kl}(u)}{S^{(0)}(\boldsymbol{\beta};u)^2}\end{aligned}$$

$$= \int_0^t \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta}, u)}{S^{(0)}(\boldsymbol{\beta}; u)} \right\} Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) \widehat{\lambda}_0(u) du.$$

Using the results in Wei et al. (1989) and Spiekerman and Lin (1998), we have

$$\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta} = \widehat{\boldsymbol{V}}_m \sum_{i=1}^{n} \sum_{j=1}^{m_i} \boldsymbol{U}_{ij}(\boldsymbol{\beta}) + o_p(n^{-\frac{1}{2}}),$$

in addition to the strong convergence of $\widehat{\boldsymbol{\beta}}$ to $\boldsymbol{\beta}$.

Thus we have

$$-\left\{ \widehat{M}_{ij}(t; \widehat{\boldsymbol{\beta}}) - \widehat{M}_{ij}(t; \boldsymbol{\beta}) \right\} = \widehat{\boldsymbol{D}}'_{ij}(t; \boldsymbol{\beta}^*)(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}) \approx \widehat{\boldsymbol{D}}'_{ij}(t; \boldsymbol{\beta}) \widehat{\boldsymbol{V}}_m \sum_{k=1}^{n} \sum_{l=1}^{m_k} \boldsymbol{U}_{kl}(\boldsymbol{\beta}).$$

The third term of (1) can be written as

$$\begin{aligned}
-\left\{ \widehat{M}_{ij}(t; \boldsymbol{\beta}) - M_{ij}(t; \boldsymbol{\beta}) \right\} &= -\left\{ N_{ij}(t) - \int_0^t Y_{ij}(u) \widehat{\lambda}_0(u; \boldsymbol{\beta}) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) du \right\} \\
&\quad + \left\{ N_{ij}(t) - \int_0^t Y_{ij}(u) \lambda_0(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) du \right\} \\
&= \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) \left\{ \widehat{\lambda}_0(u; \boldsymbol{\beta}) - \lambda_0(u) \right\} du \\
&= \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) \sum_{k=1}^{n} \sum_{l=1}^{m_k} \frac{dN_{kl}(u)}{S^{(0)}(\boldsymbol{\beta}; u)} - \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) \lambda_0(u) du \\
&= \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) S^{(0)}(\boldsymbol{\beta}; u)^{-1} \sum_{k=1}^{n} \sum_{l=1}^{m_k} dN_{kl}(u) \\
&\quad - \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) S^{(0)}(\boldsymbol{\beta}; u)^{-1} S^{(0)}(\boldsymbol{\beta}; u) \lambda_0(u) du \\
&= \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) S^{(0)}(\boldsymbol{\beta}; u)^{-1} \\
&\quad \times \left\{ \sum_{k=1}^{n} \sum_{l=1}^{m_k} dN_{kl}(u) - \sum_{k=1}^{n} \sum_{l=1}^{m_k} Y_{kl}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{kl}) \lambda_0(u) du \right\} \\
&= \int_0^t Y_{ij}(u) \exp(\boldsymbol{\beta}' \boldsymbol{Z}_{ij}) S^{(0)}(\boldsymbol{\beta}; u)^{-1} dM(u),
\end{aligned}$$

where we define $M(t) = \sum_{i=1}^{n} \sum_{j=1}^{m_i} M_{ij}(t)$ as the total sum of individual martingales.

That is, the individual martingale residual (1) can be approximated by

$$M_{ij}(t;\boldsymbol{\beta}) \approx \widehat{M}_{ij}(t;\widehat{\boldsymbol{\beta}}) + \widehat{\boldsymbol{D}}'_{ij}(t;\widehat{\boldsymbol{\beta}})\widehat{\boldsymbol{V}}_m \sum_{k=1}^{n}\sum_{l=1}^{m_k} \boldsymbol{U}_{kl}(\widehat{\boldsymbol{\beta}}) + \int_0^t Y_{ij}(u)\exp(\widehat{\boldsymbol{\beta}}'\boldsymbol{Z}_{ij})S^{(0)}(\widehat{\boldsymbol{\beta}};u)^{-1} d\widehat{M}(u).$$

Therefore, we have

$$\begin{aligned}
&\sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} dM_{ij}(u) \\
\approx &\sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} d\widehat{M}_{ij}(u;\widehat{\boldsymbol{\beta}}) \\
&+ \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} d\widehat{\boldsymbol{D}}'_{ij}(u;\widehat{\boldsymbol{\beta}})\widehat{\boldsymbol{V}}_m \sum_{k=1}^{n}\sum_{l=1}^{m_k} \boldsymbol{U}_{kl}(\widehat{\boldsymbol{\beta}}) \\
&+ \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} Y_{ij}(u)\exp(\widehat{\boldsymbol{\beta}}'\boldsymbol{Z}_{ij})S^{(0)}(\widehat{\boldsymbol{\beta}};u)^{-1} d\widehat{M}(u) \\
= &\widehat{\boldsymbol{U}}_i + \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} d\widehat{\boldsymbol{D}}'_{ij}(u;\widehat{\boldsymbol{\beta}})\widehat{\boldsymbol{V}}_m \sum_{k=1}^{n}\sum_{l=1}^{m_k} \boldsymbol{U}_{kl}(\widehat{\boldsymbol{\beta}}) \\
&+ \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} Y_{ij}(u)\exp(\widehat{\boldsymbol{\beta}}'\boldsymbol{Z}_{ij})S^{(0)}(\widehat{\boldsymbol{\beta}};u)^{-1} d\widehat{M}(u).
\end{aligned}$$

Eliminating mean-zero cross-product terms, we define the following bias-corrected version of the estimated martingale-score $\widehat{\boldsymbol{U}}_i$:

$$\begin{aligned}
\widehat{\boldsymbol{U}}_i^{BC} = &\widehat{\boldsymbol{U}}_i + \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} d\widehat{\boldsymbol{D}}'_{ij}(u;\widehat{\boldsymbol{\beta}})\widehat{\boldsymbol{V}}_m \sum_{l=1}^{m_i} \boldsymbol{U}_{il}(\widehat{\boldsymbol{\beta}}) \\
&+ \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} Y_{ij}(u)\exp(\widehat{\boldsymbol{\beta}}'\boldsymbol{Z}_{ij})S^{(0)}(\widehat{\boldsymbol{\beta}};u)^{-1} d\widehat{M}_{\boldsymbol{i\bullet}}(u) \\
= &\left\{ \boldsymbol{I} + \sum_{j=1}^{m_i} \int_0^\infty \left\{ \boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)} \right\} d\widehat{\boldsymbol{D}}'_{ij}(u;\widehat{\boldsymbol{\beta}})\widehat{\boldsymbol{V}}_m \right\} \widehat{\boldsymbol{U}}_i
\end{aligned}$$

$$+\sum_{j=1}^{m_i}\int_0^\infty \left\{\boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\widehat{\boldsymbol{\beta}};u)}{S^{(0)}(\widehat{\boldsymbol{\beta}};u)}\right\} Y_{ij}(u)\exp(\widehat{\boldsymbol{\beta}}'\boldsymbol{Z}_{ij})S^{(0)}(\widehat{\boldsymbol{\beta}};u)^{-1}d\widehat{M_{i\bullet}}(u),$$

where $M_{i\bullet}(t)=\sum_{j=1}^{m_i} M_{ij}(t)$ is the sum of within-cluster martingales.

Finally, we have

$$\widehat{\boldsymbol{V}}_{MR} = \widehat{\boldsymbol{V}}_m \left\{\sum_{i=1}^{n} \widehat{\boldsymbol{U}}_i^{BC}\left(\widehat{\boldsymbol{U}}_i^{BC}\right)'\right\}\widehat{\boldsymbol{V}}_m.$$

Web Appendix B

Derivation of Equation (8) in the manuscript

By the first-order Taylor expansion, we have

$$\boldsymbol{U}_i \approx \widehat{\boldsymbol{U}}_i - \widehat{\boldsymbol{\Omega}}_i\left(\boldsymbol{\beta}-\widehat{\boldsymbol{\beta}}\right), \tag{2}$$

where

$$\begin{aligned}
\boldsymbol{\Omega}_i =& -\frac{\partial \boldsymbol{U}_i}{\partial \boldsymbol{\beta}} = -\frac{\partial}{\partial \boldsymbol{\beta}}\sum_{j=1}^{m_i}\int_0^\infty \left\{\boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)}\right\} dM_{ij}(u)\\
=& -\frac{\partial}{\partial \boldsymbol{\beta}}\sum_{j=1}^{m_i}\int_0^\infty \left\{\boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)}\right\} dN_{ij}(u)\\
&+\frac{\partial}{\partial \boldsymbol{\beta}}\sum_{j=1}^{m_i}\int_0^\infty \left\{\boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)}\right\} Y_{ij}(u)\lambda_0(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})du\\
=&\sum_{j=1}^{m_i}\int_0^\infty \left\{\frac{\boldsymbol{S}^{(2)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)'}{S^{(0)}(\boldsymbol{\beta};u)^2}\right\} dN_{ij}(u)\\
&-\sum_{j=1}^{m_i}\int_0^\infty \left\{\frac{\boldsymbol{S}^{(2)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)'}{S^{(0)}(\boldsymbol{\beta};u)^2}\right\} Y_{ij}(u)\lambda_0(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})du\\
&+\sum_{j=1}^{m_i}\int_0^\infty \left\{\boldsymbol{Z}_{ij} - \frac{\boldsymbol{S}^{(1)}(\boldsymbol{\beta};u)}{S^{(0)}(\boldsymbol{\beta};u)}\right\} \boldsymbol{Z}_{ij}'Y_{ij}(u)\lambda_0(u)\exp(\boldsymbol{\beta}'\boldsymbol{Z}_{ij})du,
\end{aligned}$$

and the hat notation indicates that the evaluation is at the estimator $\widehat{\boldsymbol{\beta}}$. By summing across all clusters and re-arranging terms, we obtain

$$\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta} \approx \widehat{\boldsymbol{V}}_m \left(\sum_{i=1}^{n} \boldsymbol{U}_i \right), \tag{3}$$

where $\widehat{\boldsymbol{V}}_m = (\sum_{i=1}^{n} \widehat{\boldsymbol{\Omega}}_i)^{-1}$ is the model-based variance estimator. If for small changes in $\widehat{\boldsymbol{\beta}}$, $\widehat{\boldsymbol{V}}_m$ is approximately constant, then we can use the sandwich estimator $\widehat{\boldsymbol{V}}_s = \widehat{\boldsymbol{V}}_m \left(\sum_{i=1}^{n} \widehat{\boldsymbol{U}}_i \widehat{\boldsymbol{U}}_i' \right) \widehat{\boldsymbol{V}}_m$ to estimate the variance of $\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}$.

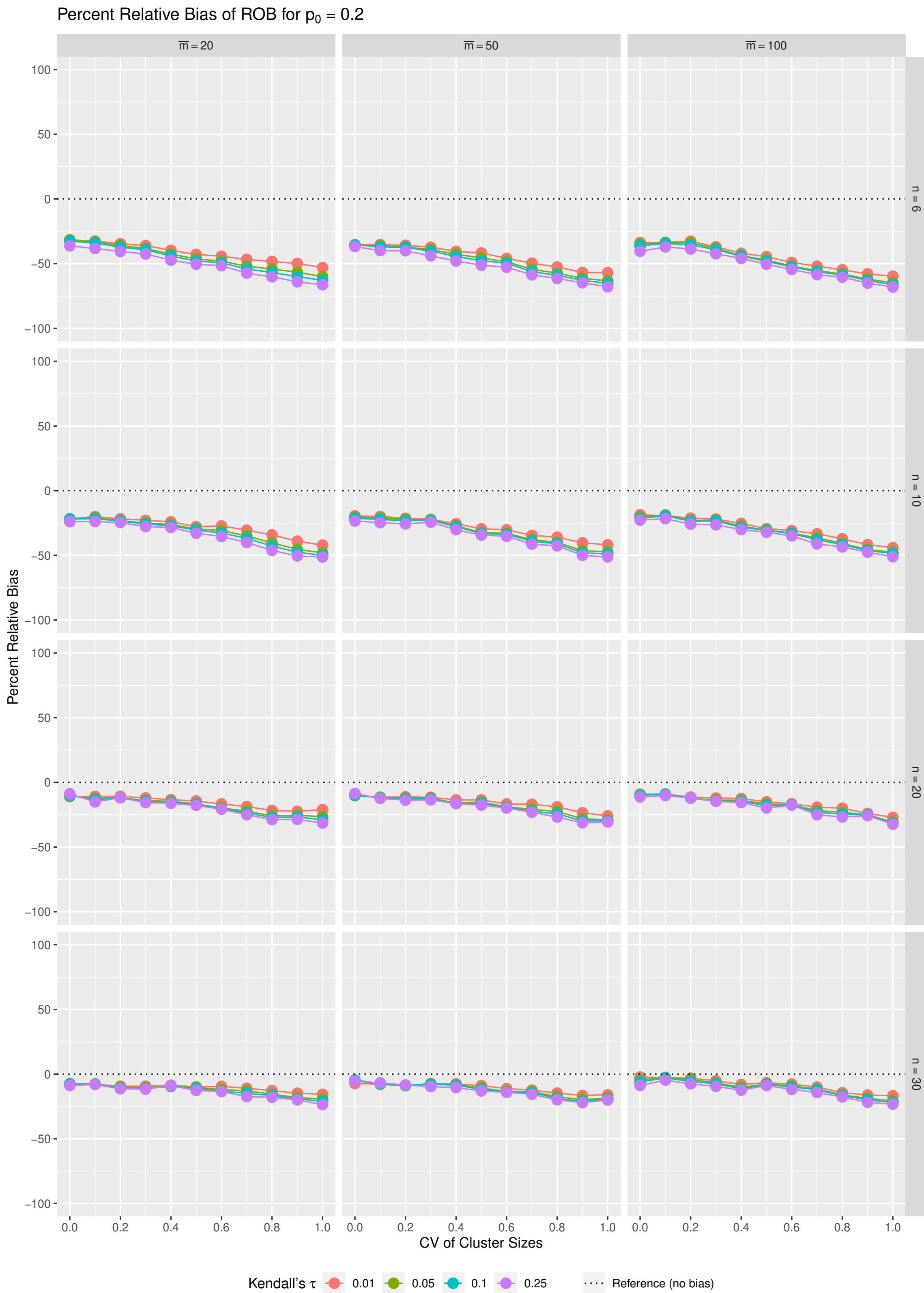
By (2) and (3), we have

$$\begin{aligned}
\widehat{\boldsymbol{U}}_i \widehat{\boldsymbol{U}}_i' \approx & \left\{ \boldsymbol{U}_i + \widehat{\boldsymbol{\Omega}}_i \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right) \right\} \left\{ \boldsymbol{U}_i + \widehat{\boldsymbol{\Omega}}_i \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right) \right\}' \\
= & \boldsymbol{U}_i \boldsymbol{U}_i' + \boldsymbol{U}_i \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right)' \widehat{\boldsymbol{\Omega}}_i' + \widehat{\boldsymbol{\Omega}}_i \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right) \boldsymbol{U}_i + \widehat{\boldsymbol{\Omega}}_i \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right) \left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}} \right)' \widehat{\boldsymbol{\Omega}}_i' \\
\approx & \boldsymbol{U}_i \boldsymbol{U}_i' - \boldsymbol{U}_i \left(\sum_{i=1}^{n} \boldsymbol{U}_i' \right) \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i' - \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \left(\sum_{i=1}^{n} \boldsymbol{U}_i \right) \boldsymbol{U}_i \\
& + \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \left(\sum_{i=1}^{n} \boldsymbol{U}_i \right) \left(\sum_{i=1}^{n} \boldsymbol{U}_i' \right) \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i', \\
\mathrm{E}\left(\widehat{\boldsymbol{U}}_i \widehat{\boldsymbol{U}}_i' \right) \approx & \boldsymbol{\Psi}_i - \boldsymbol{\Psi}_i \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i' - \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \boldsymbol{\Psi}_i + \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \boldsymbol{\Psi}_i \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i' + \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \left(\sum_{j \neq i} \boldsymbol{\Psi}_j \right) \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i' \\
= & \left(\boldsymbol{I} - \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \right) \boldsymbol{\Psi}_i \left(\boldsymbol{I} - \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \right)' + \widehat{\boldsymbol{\Omega}}_i \widehat{\boldsymbol{V}}_m \left(\sum_{j \neq i} \boldsymbol{\Psi}_j \right) \widehat{\boldsymbol{V}}_m' \widehat{\boldsymbol{\Omega}}_i', \qquad (4)
\end{aligned}$$

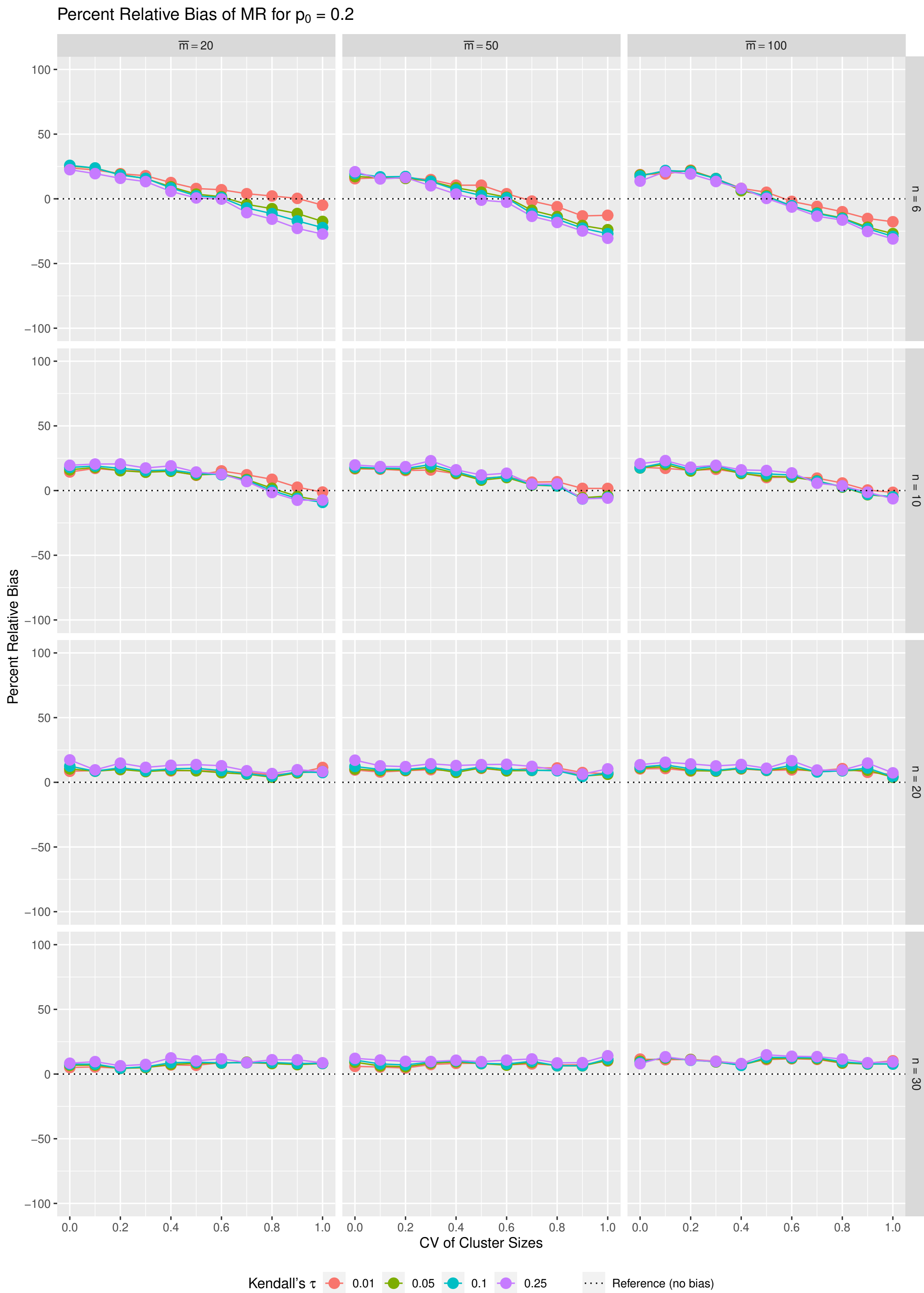
where $\boldsymbol{\Psi}_i = \mathrm{Cov}(\boldsymbol{U}_i) = \mathrm{E}\left(\boldsymbol{U}_i \boldsymbol{U}_i' \right)$ is the true covariance of the cluster-specific score.

Web Appendix C: Web figures from the main simulation study for $p_0 = 0.2$

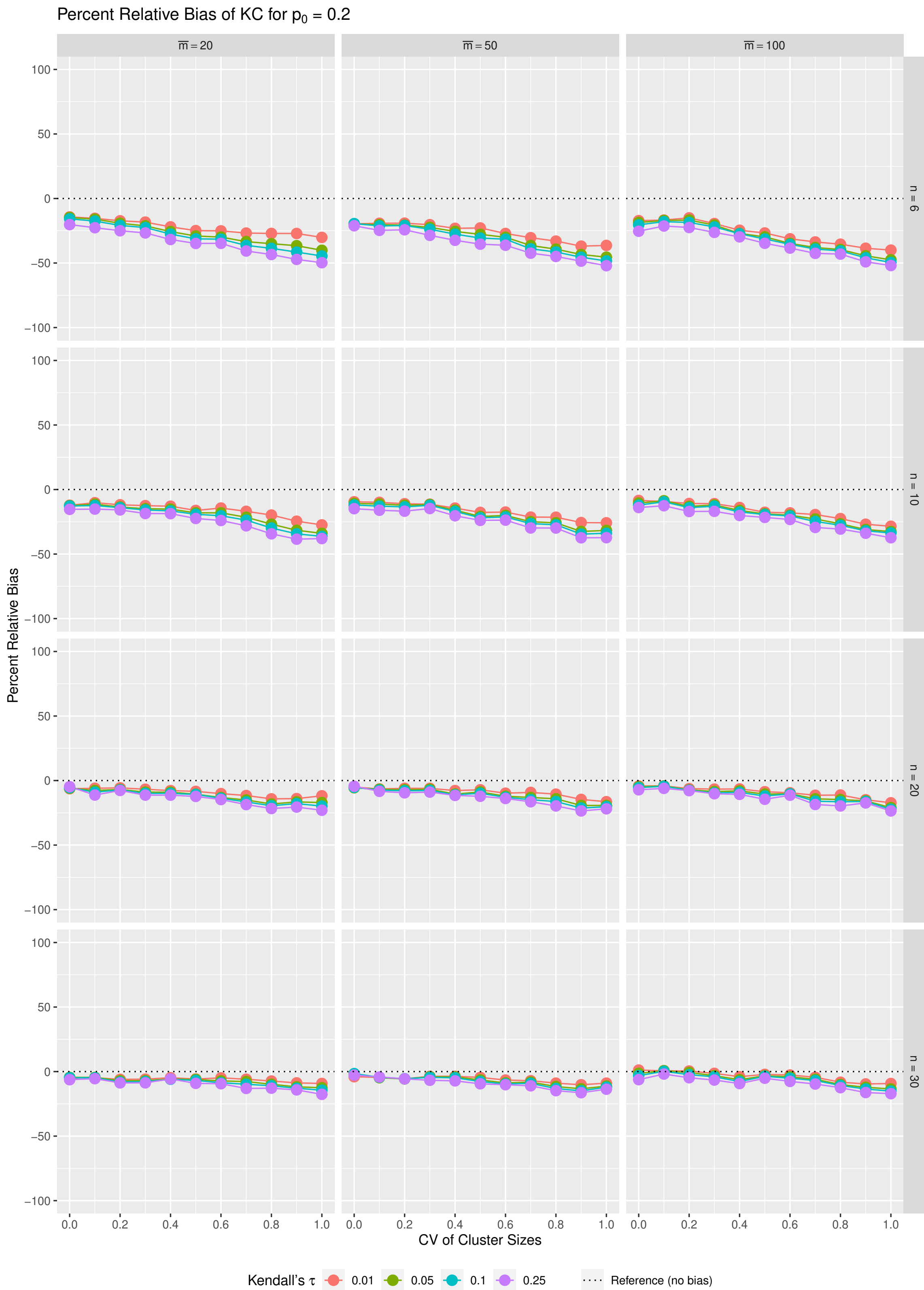
- Web Figures 1-10 present the results for the percent relative bias of different variance estimators for $p_0 = 0.2$.
  - Web Figure 1 (Page 7) refers to the ROB variance estimator.
  - Web Figure 2 (Page 8) refers to the MR variance estimator.
  - Web Figures 3, 4, 5, and 6 (Page 9-12) refer to the KC, FG, MD, and MBN variance estimators, respectively.
  - Web Figures 7, 8, 9, and 10 (Page 13-16) refer to the KCMR, FGMR, MDMR, and MBNMR variance estimators, respectively.
- Web Figures 11-20 present the results for empirical type I error rates based on different variance estimators for $p_0 = 0.2$.
  - Web Figure 11 (Page 17) refers to the ROB variance estimator.
  - Web Figure 12 (Page 18) refers to the MR variance estimator.
  - Web Figures 13, 14, 15, and 16 (Page 19-22) refer to the KC, FG, MD, and MBN variance estimators, respectively.
  - Web Figures 17, 18, 19, and 20 (Page 23-26) refer to the KCMR, FGMR, MDMR, and MBNMR variance estimators, respectively.



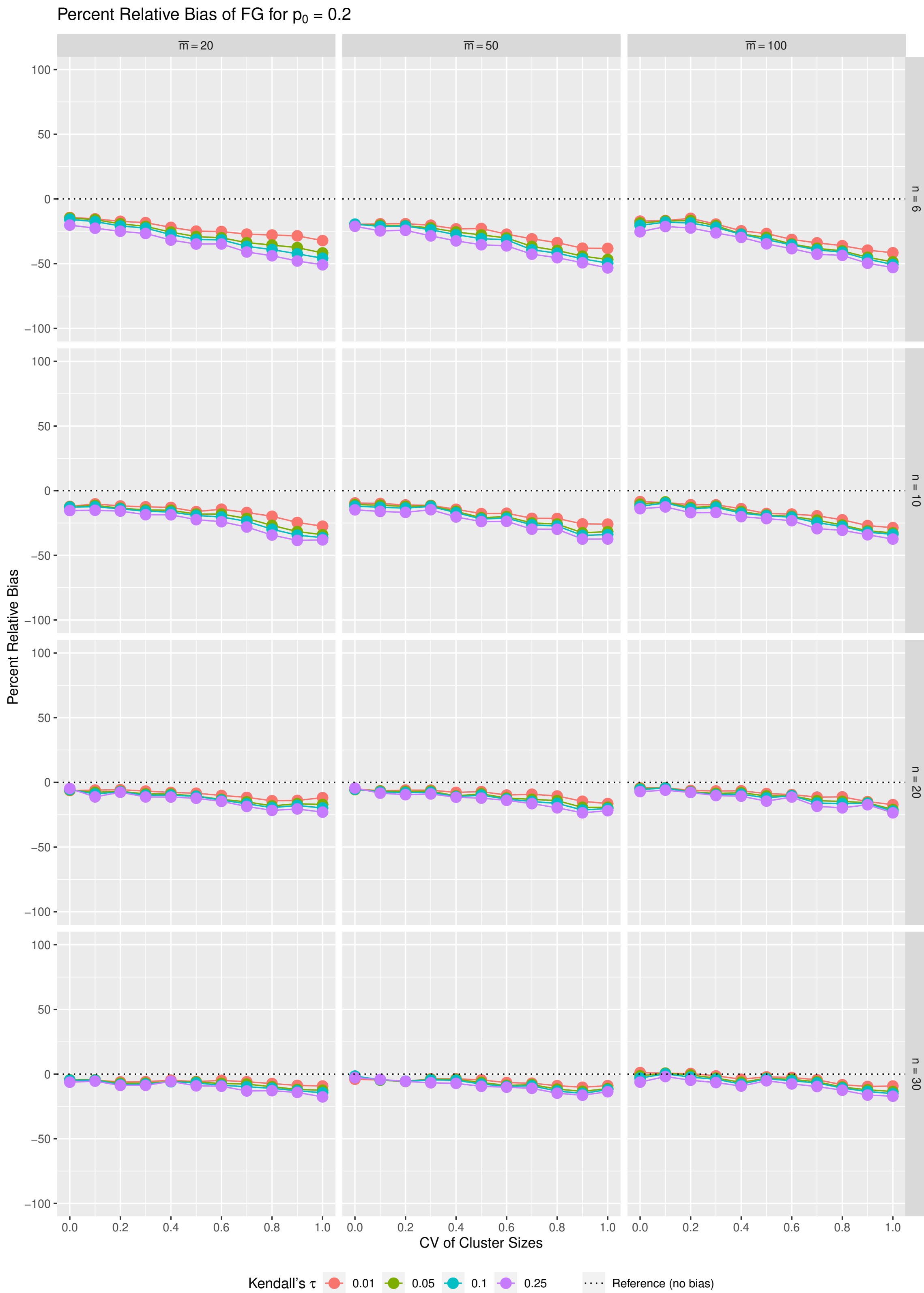
Web Figure 1: Percent relative bias of the uncorrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



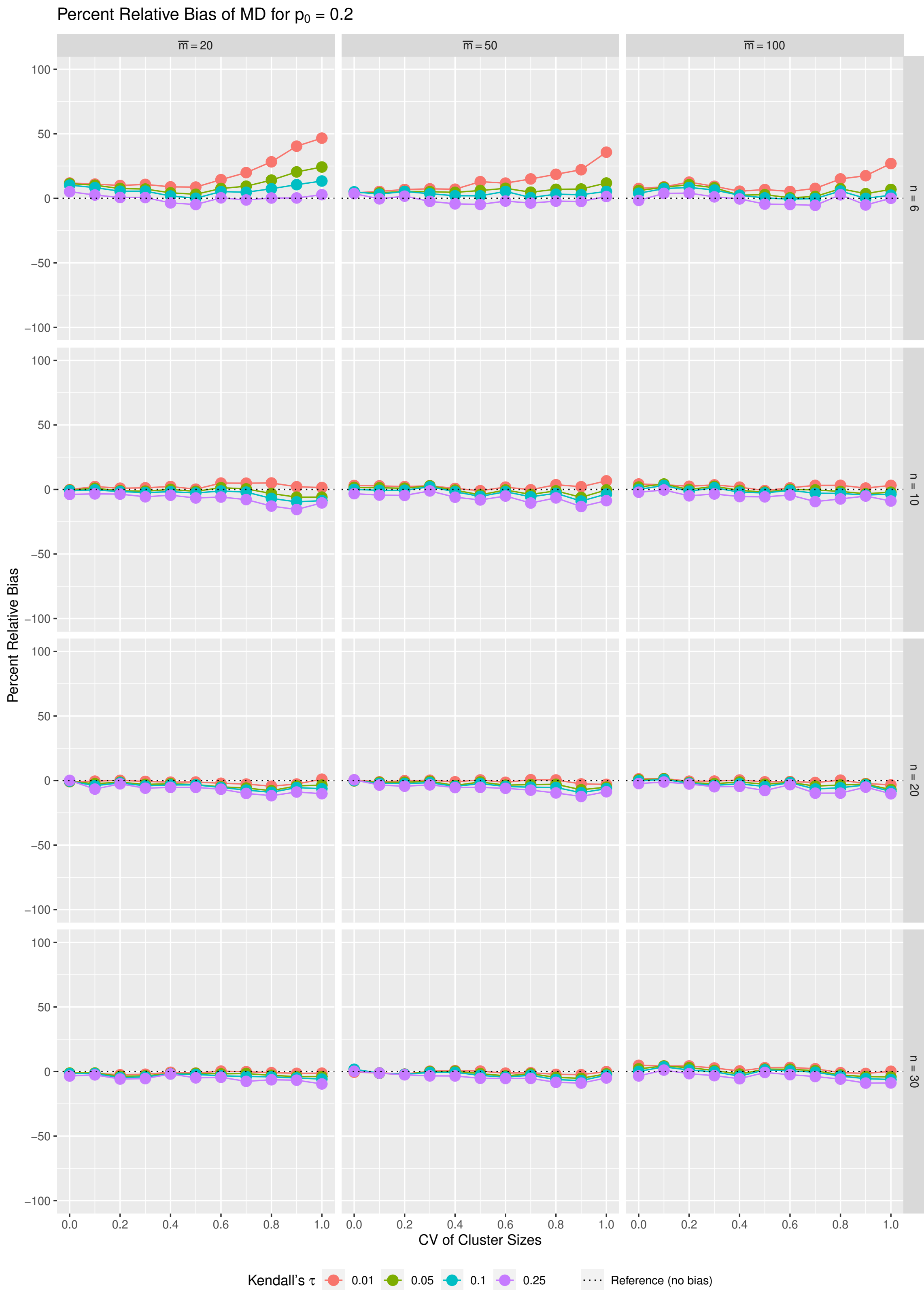
Web Figure 2: Percent relative bias of the martingale residual-based bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



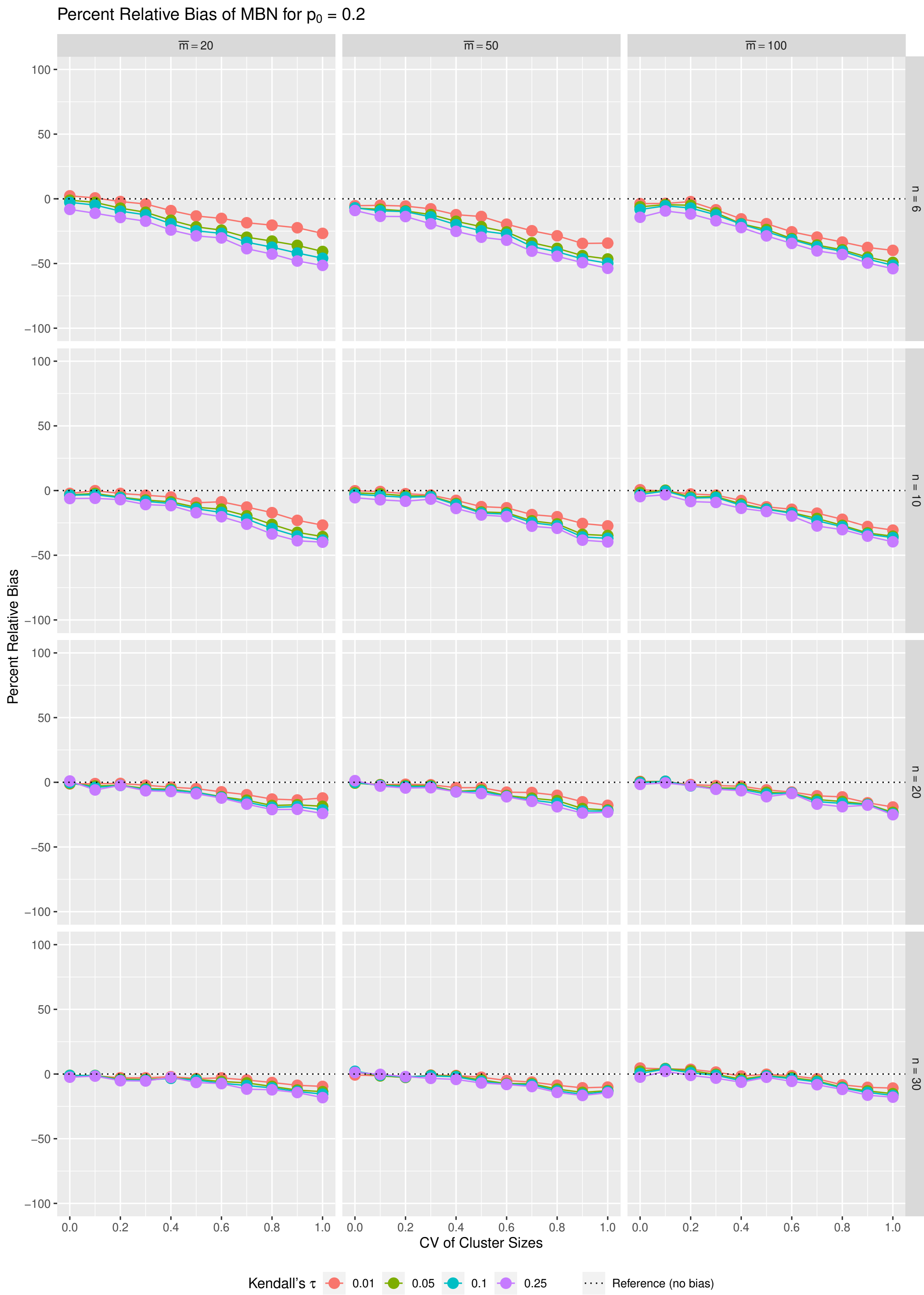
Web Figure 3: Percent relative bias of the KC bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



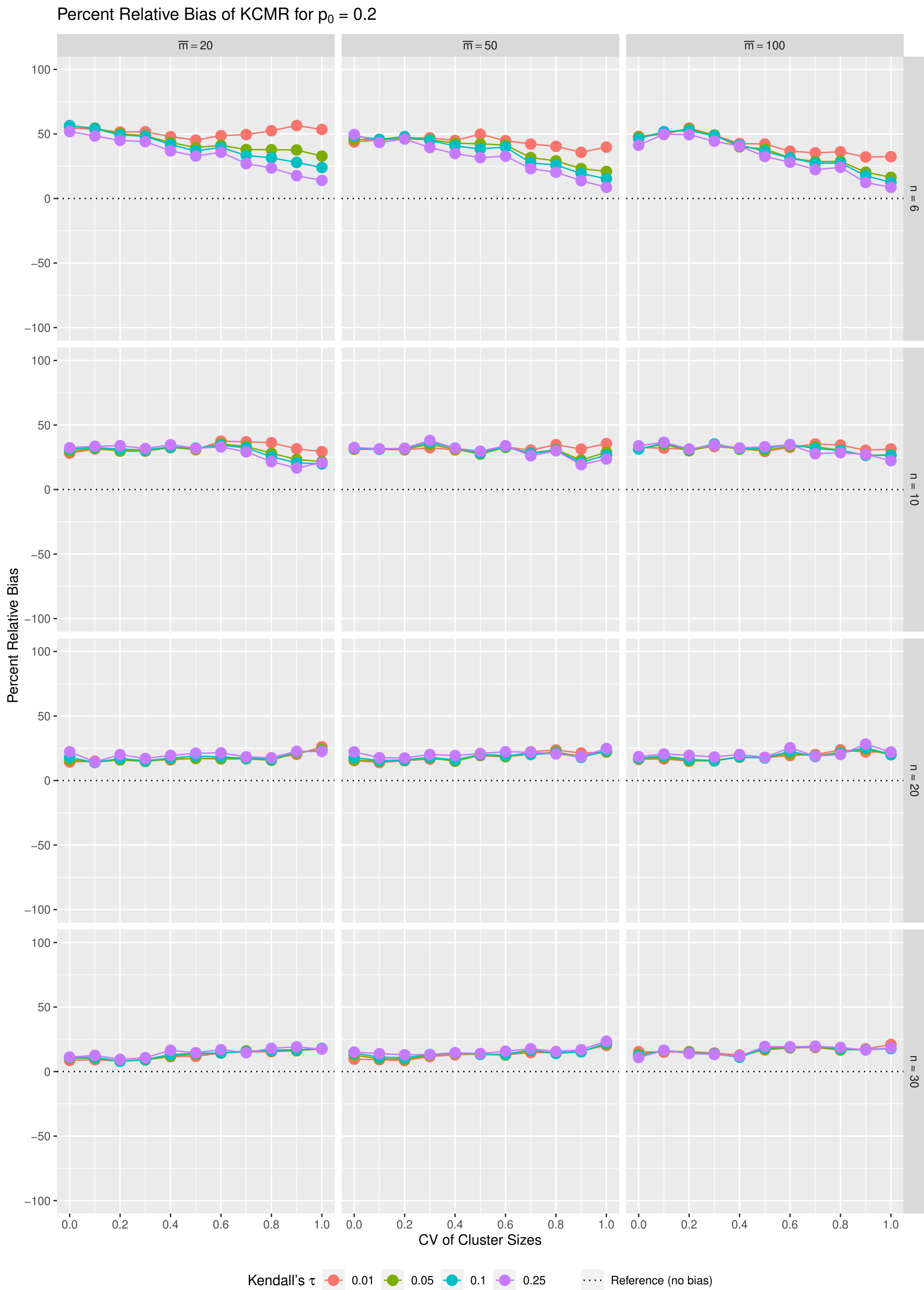
Web Figure 4: Percent relative bias of the FG bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



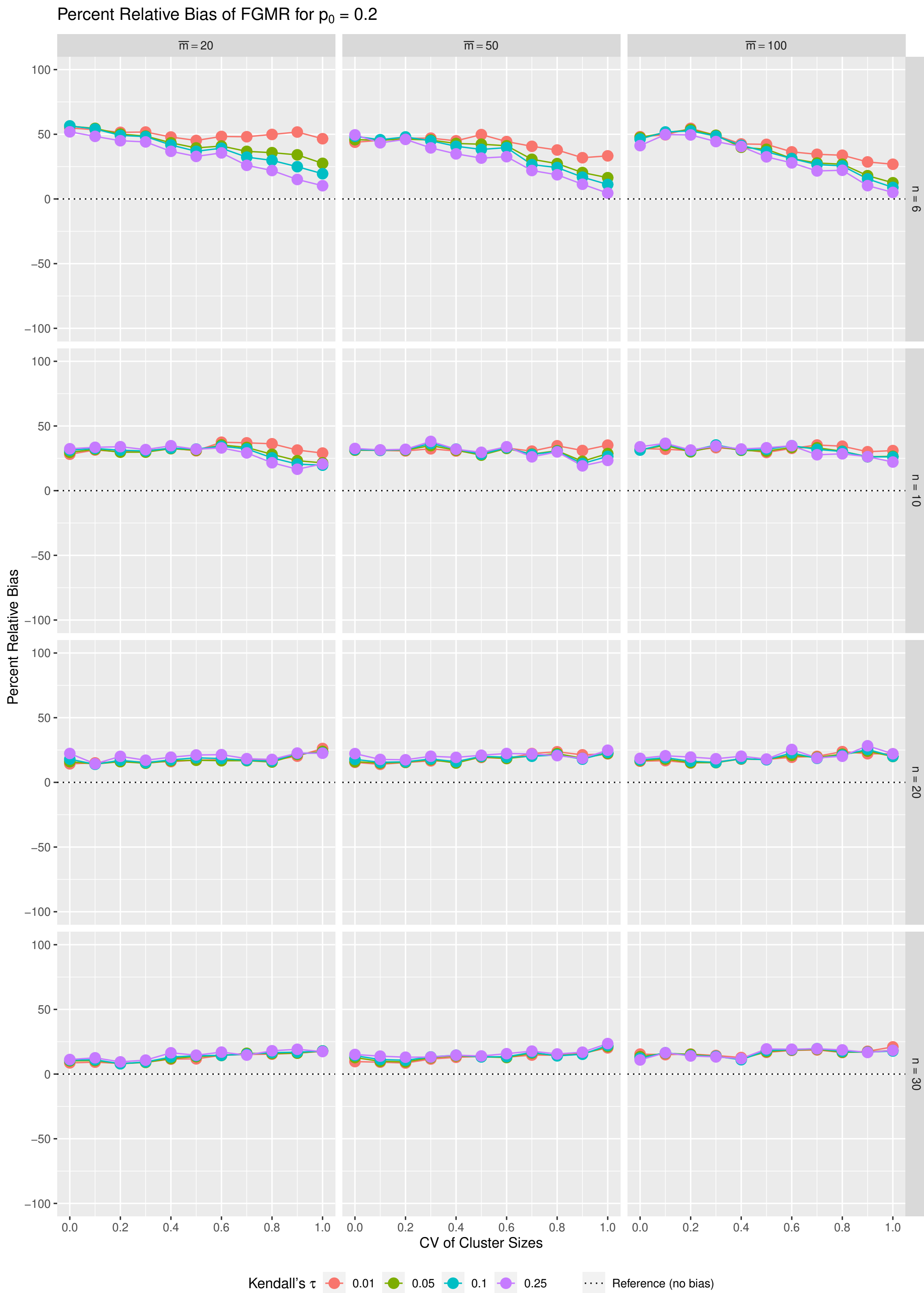
Web Figure 5: Percent relative bias of the MD bias-corrected sandwich estimator, for $p_0 = 0.2$ under the marginal Cox model.



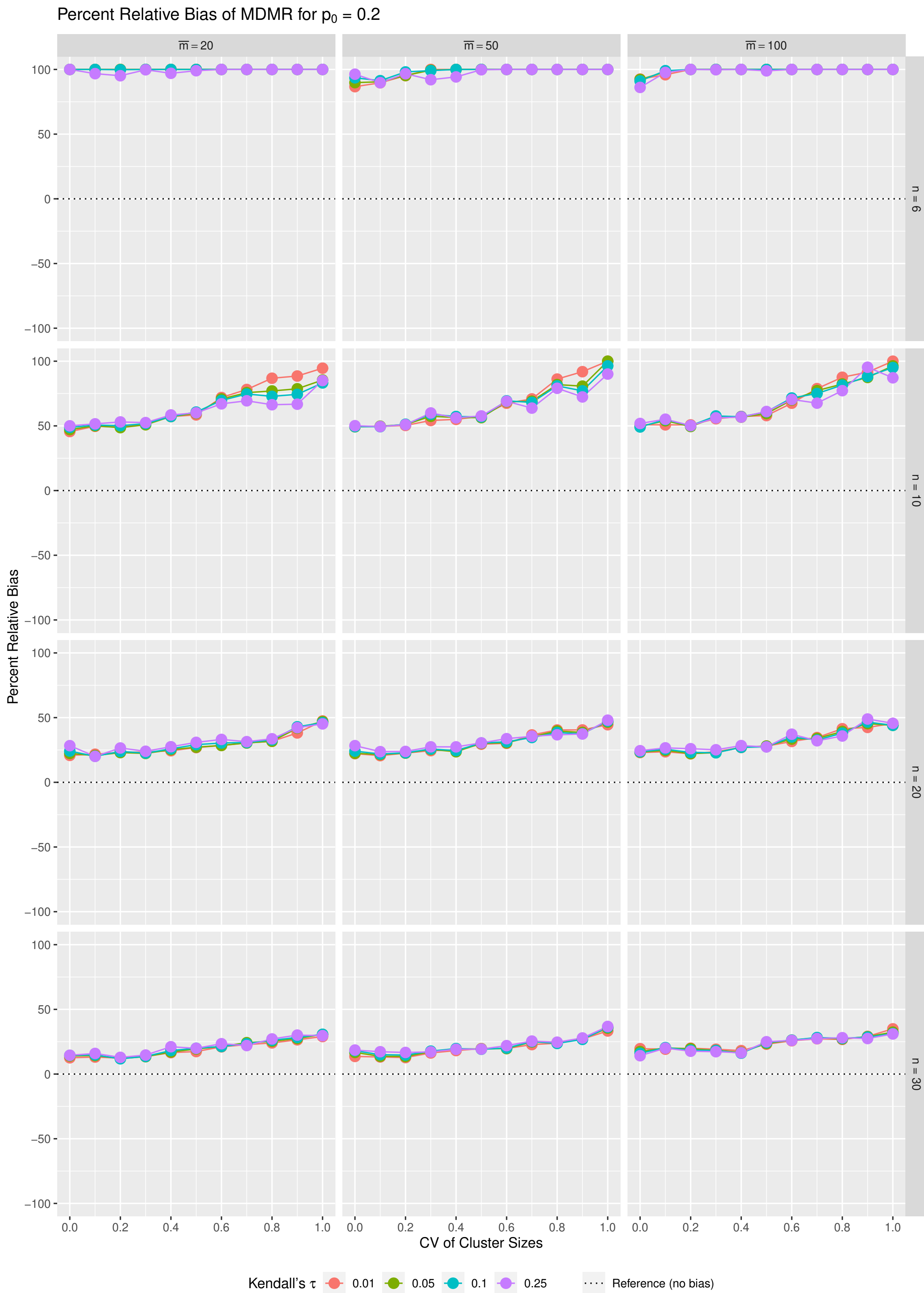
Web Figure 6: Percent relative bias of the MBN bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



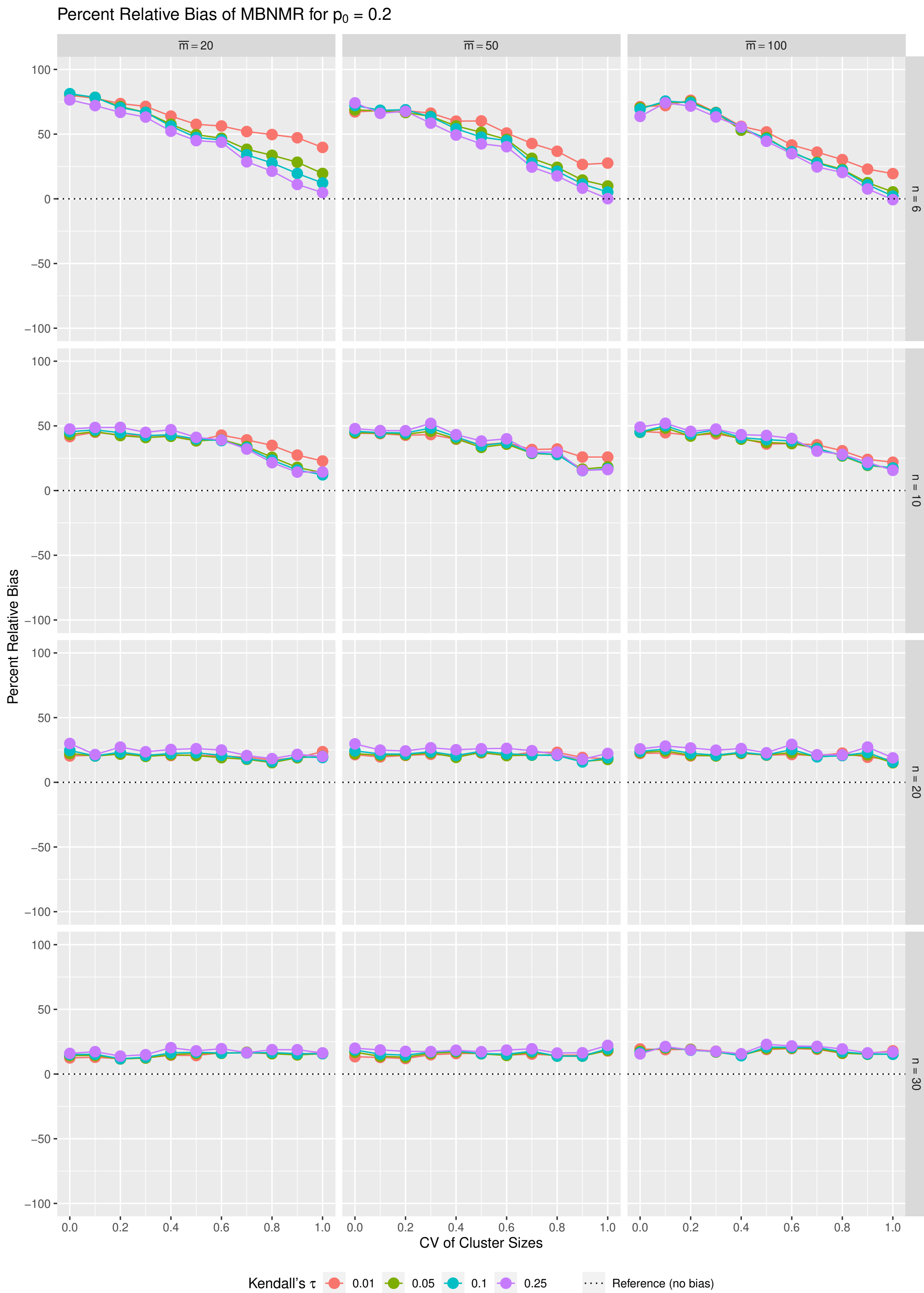
Web Figure 7: Percent relative bias of the KCMR bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



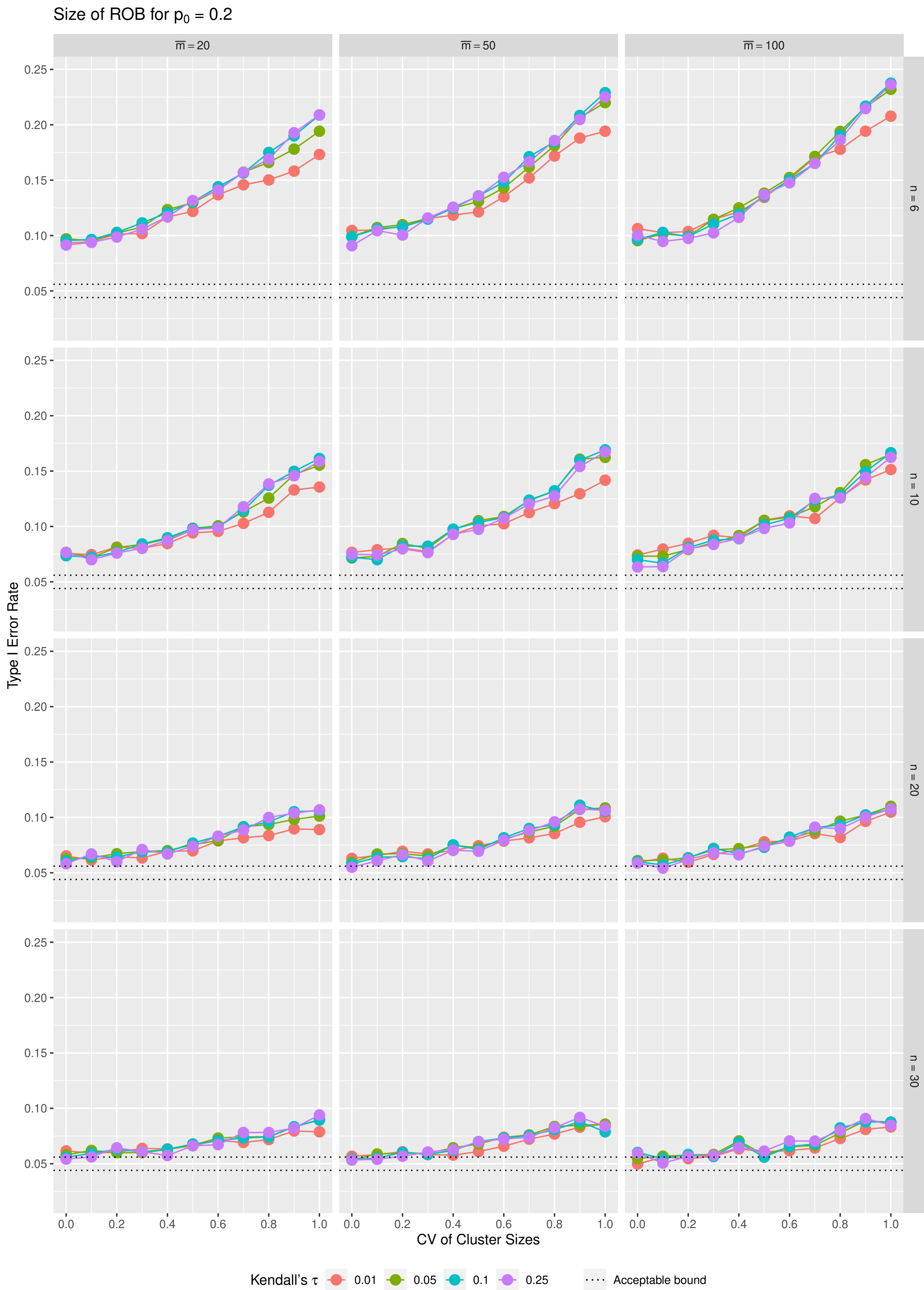
Web Figure 8: Percent relative bias of the FGMR bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



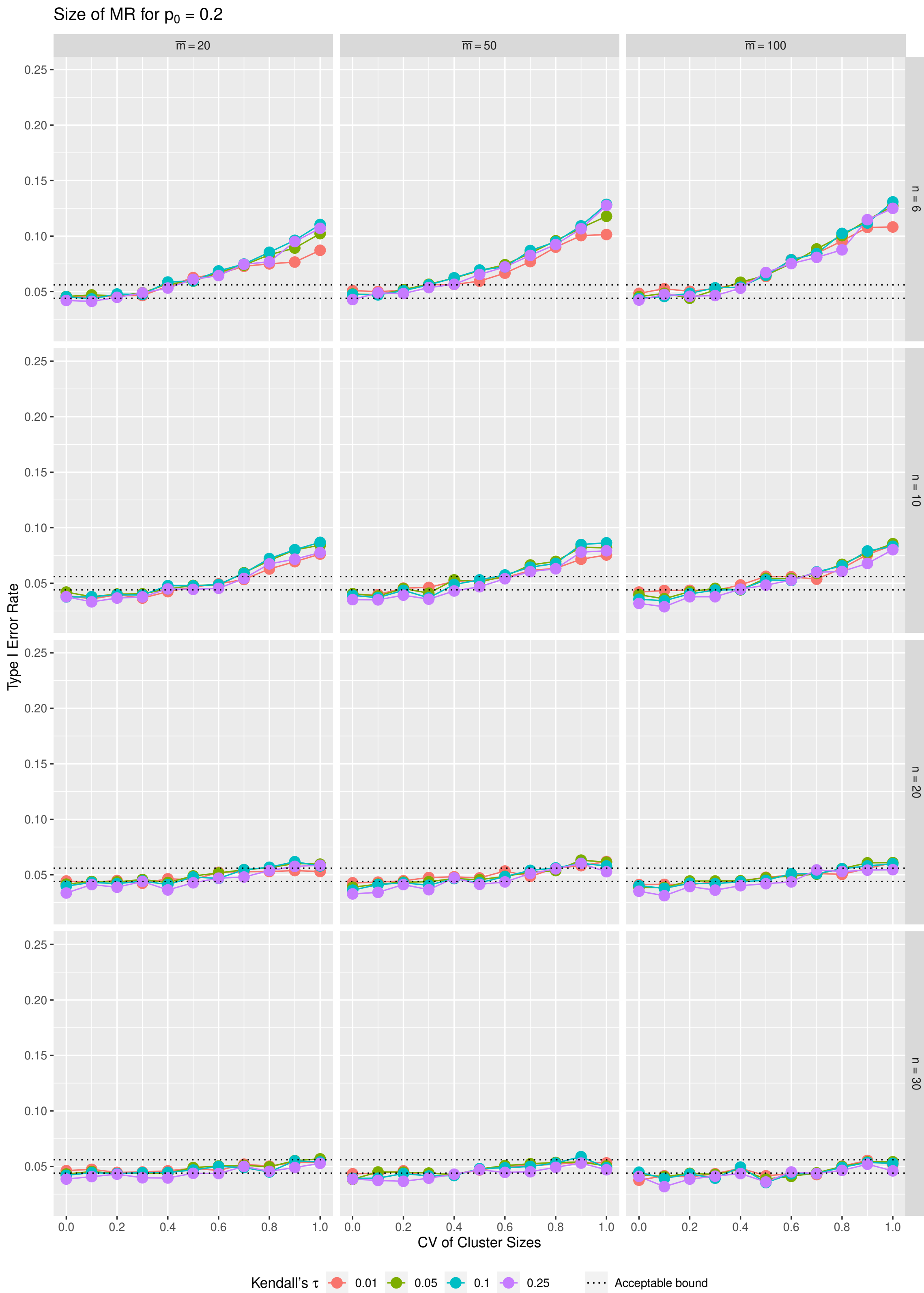
Web Figure 9: Percent relative bias of the MDMR bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



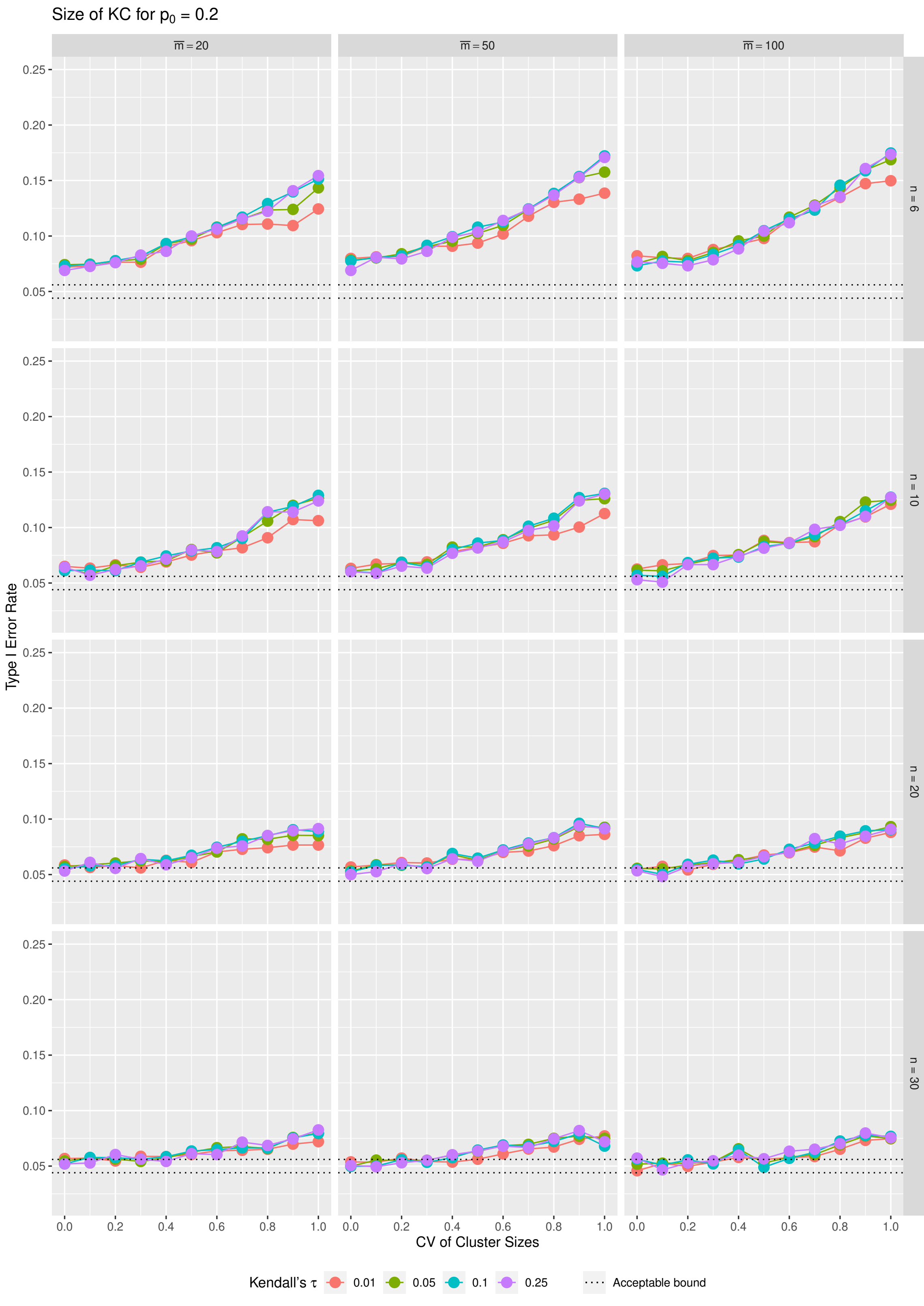
Web Figure 10: Percent relative bias of the MBNMR bias-corrected sandwich variance estimator, for $p_0 = 0.2$ under the marginal Cox model.



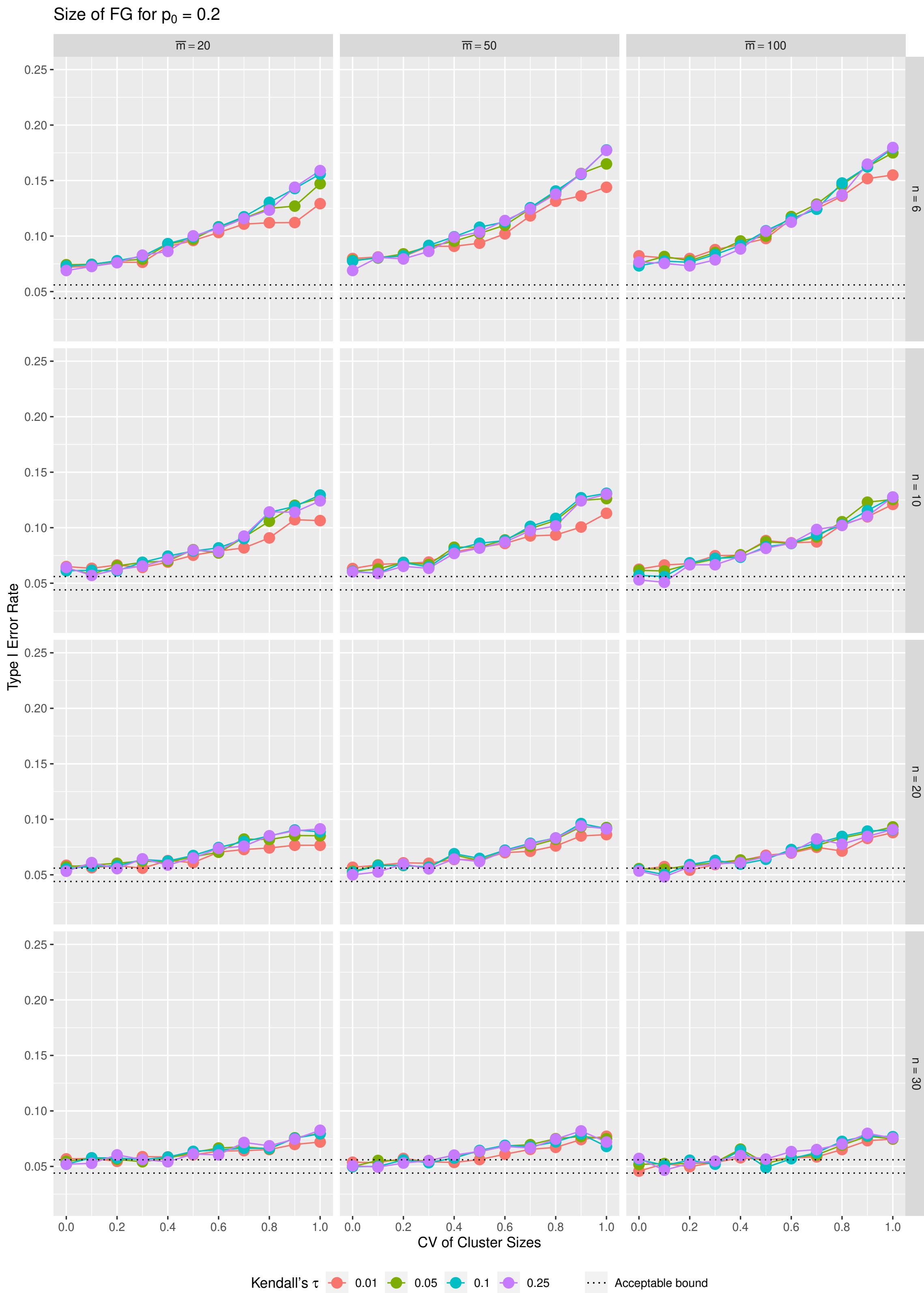
Web Figure 11: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the uncorrected sandwich variance estimator.



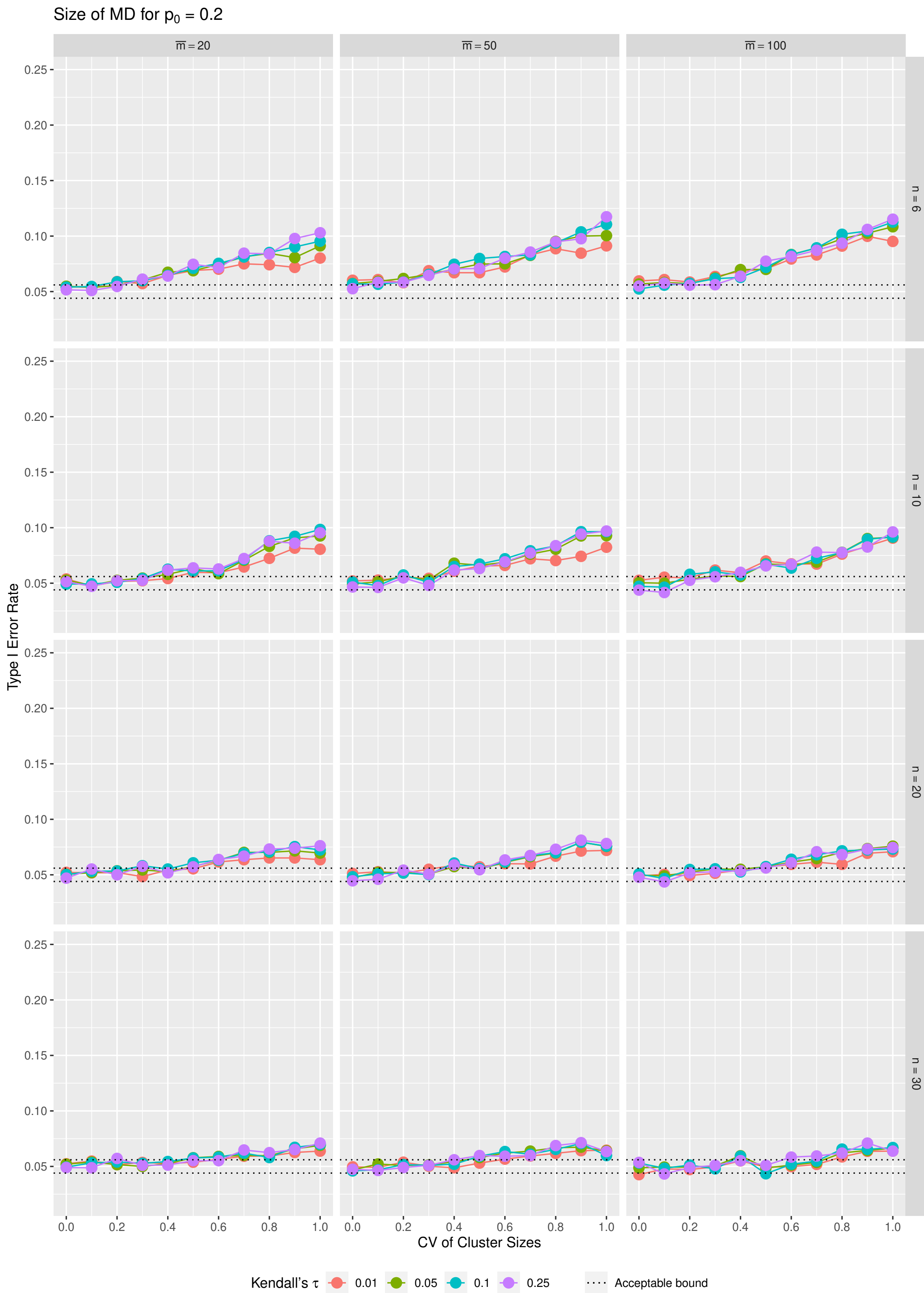
Web Figure 12: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the martingale residual-based bias-corrected sandwich variance estimator.



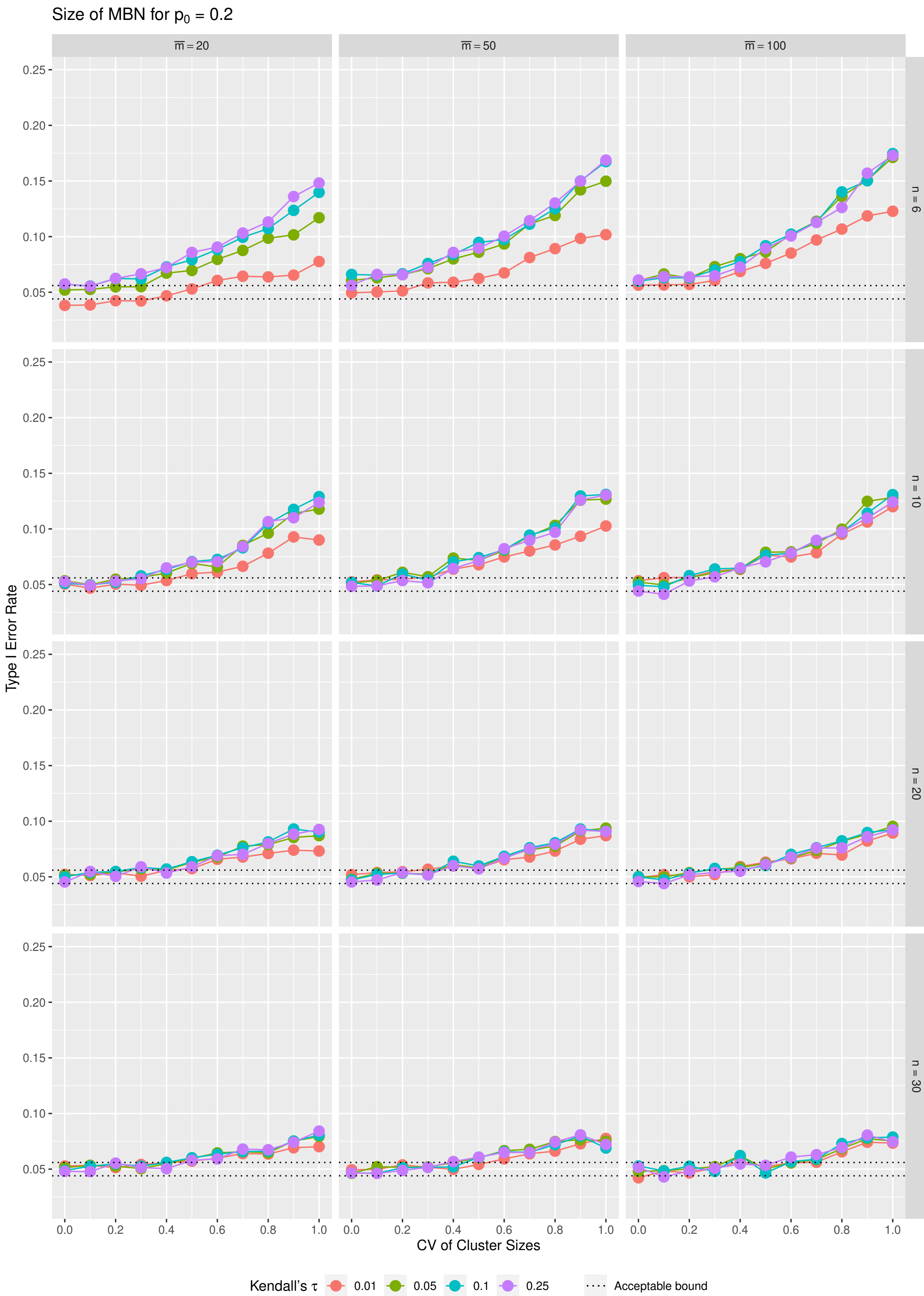
Web Figure 13: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the KC bias-corrected sandwich variance estimator.



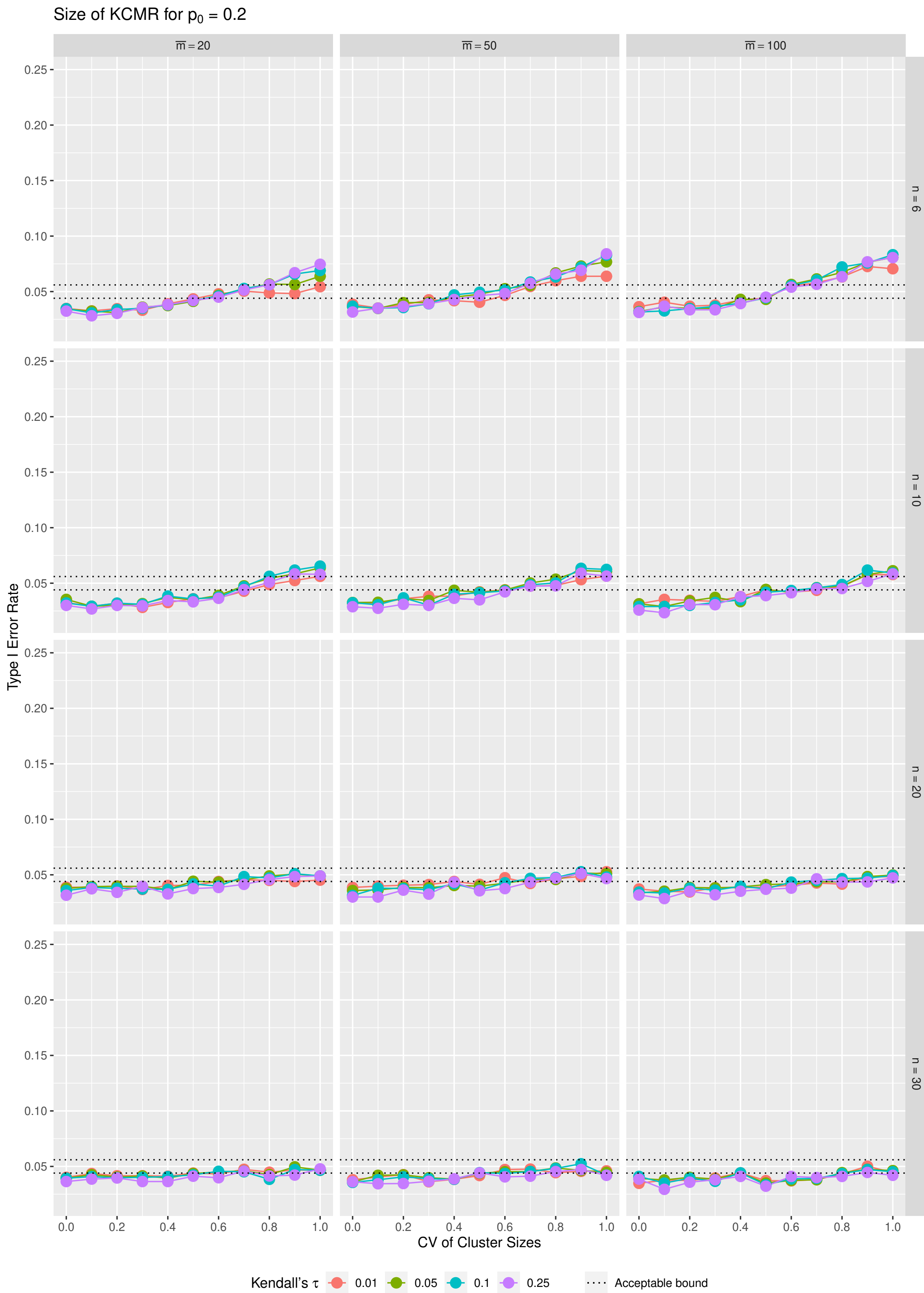
Web Figure 14: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the FG bias-corrected sandwich variance estimator.



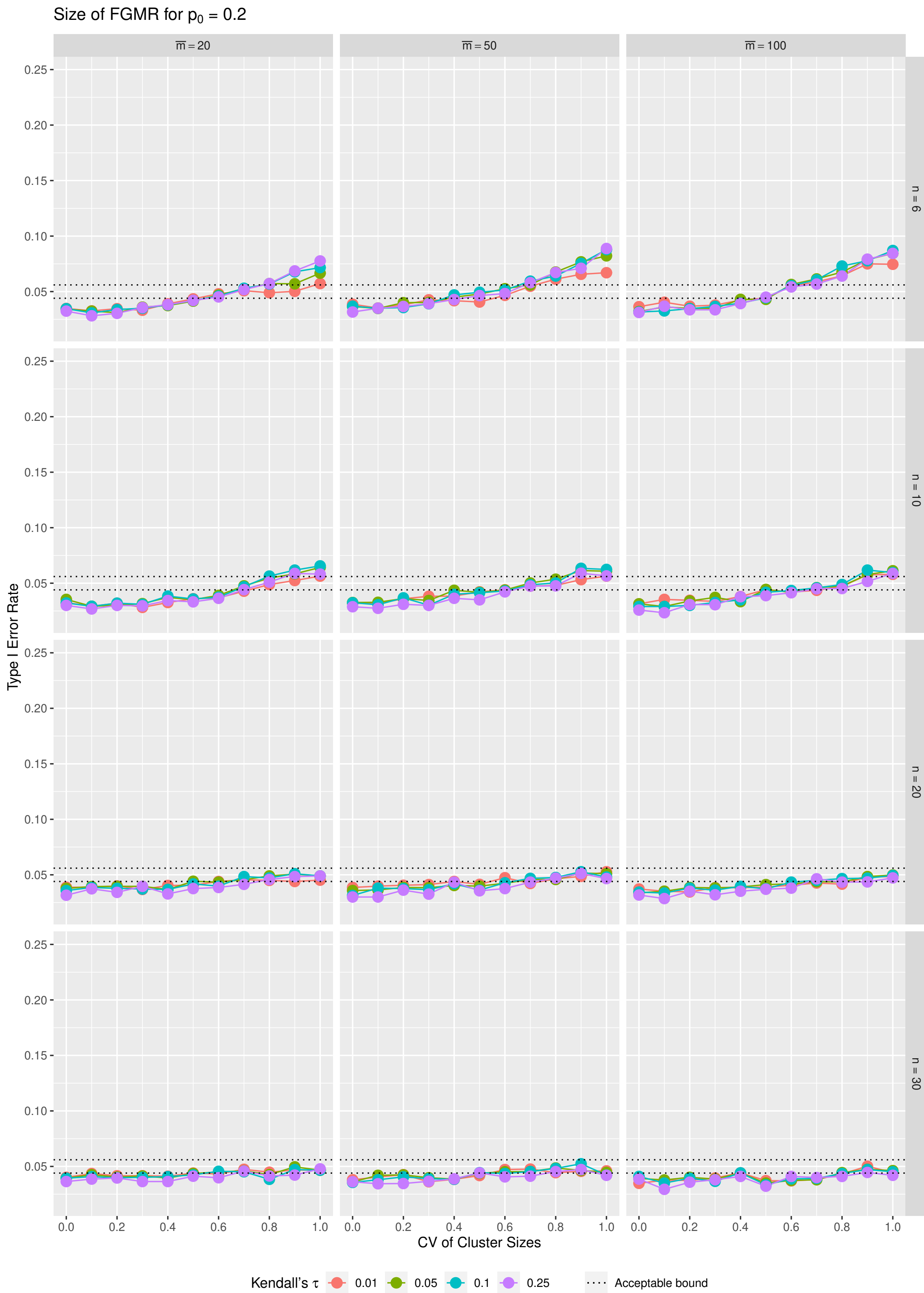
Web Figure 15: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the MD bias-corrected sandwich estimator.



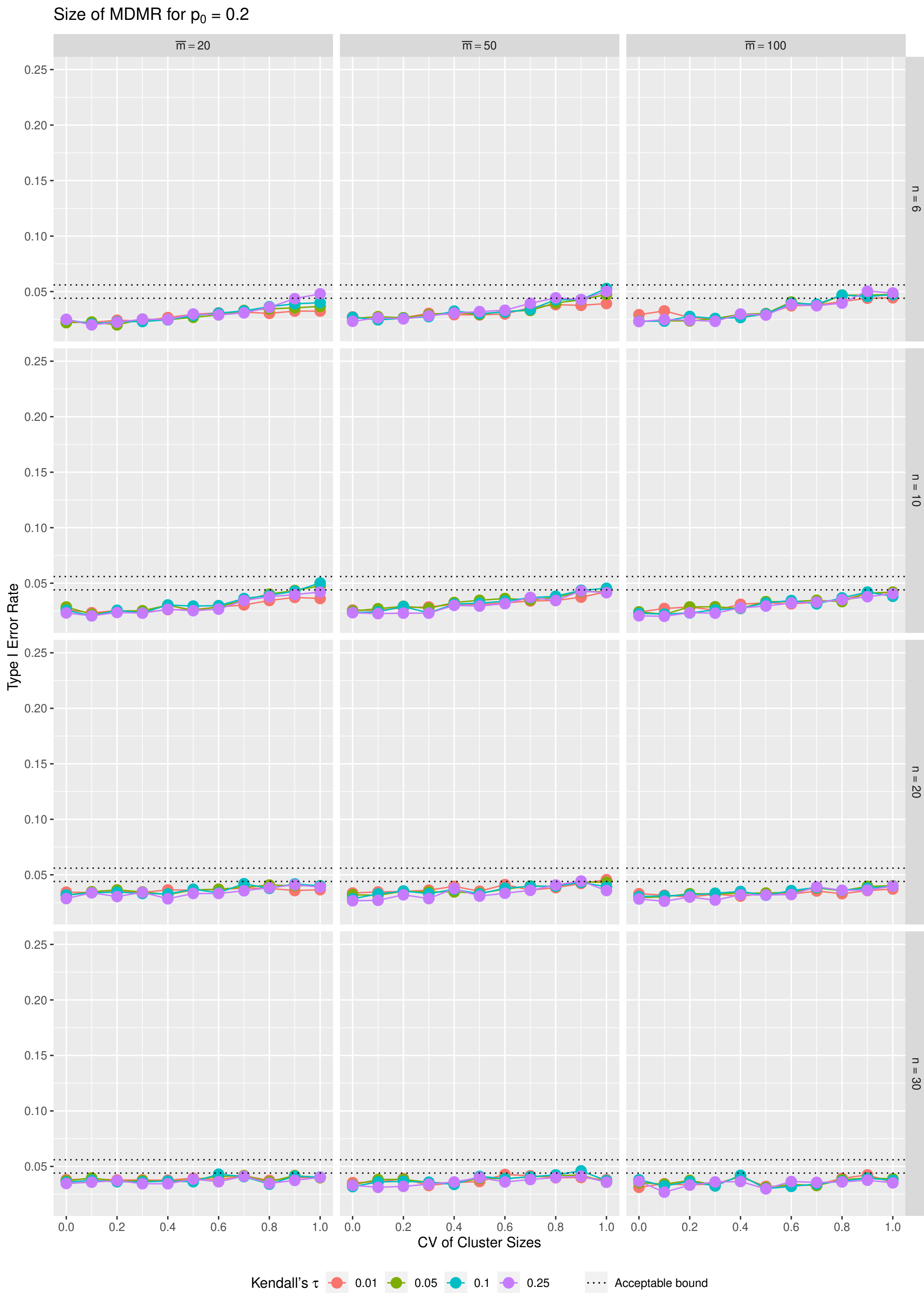
Web Figure 16: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the MBN bias-corrected sandwich variance estimator.



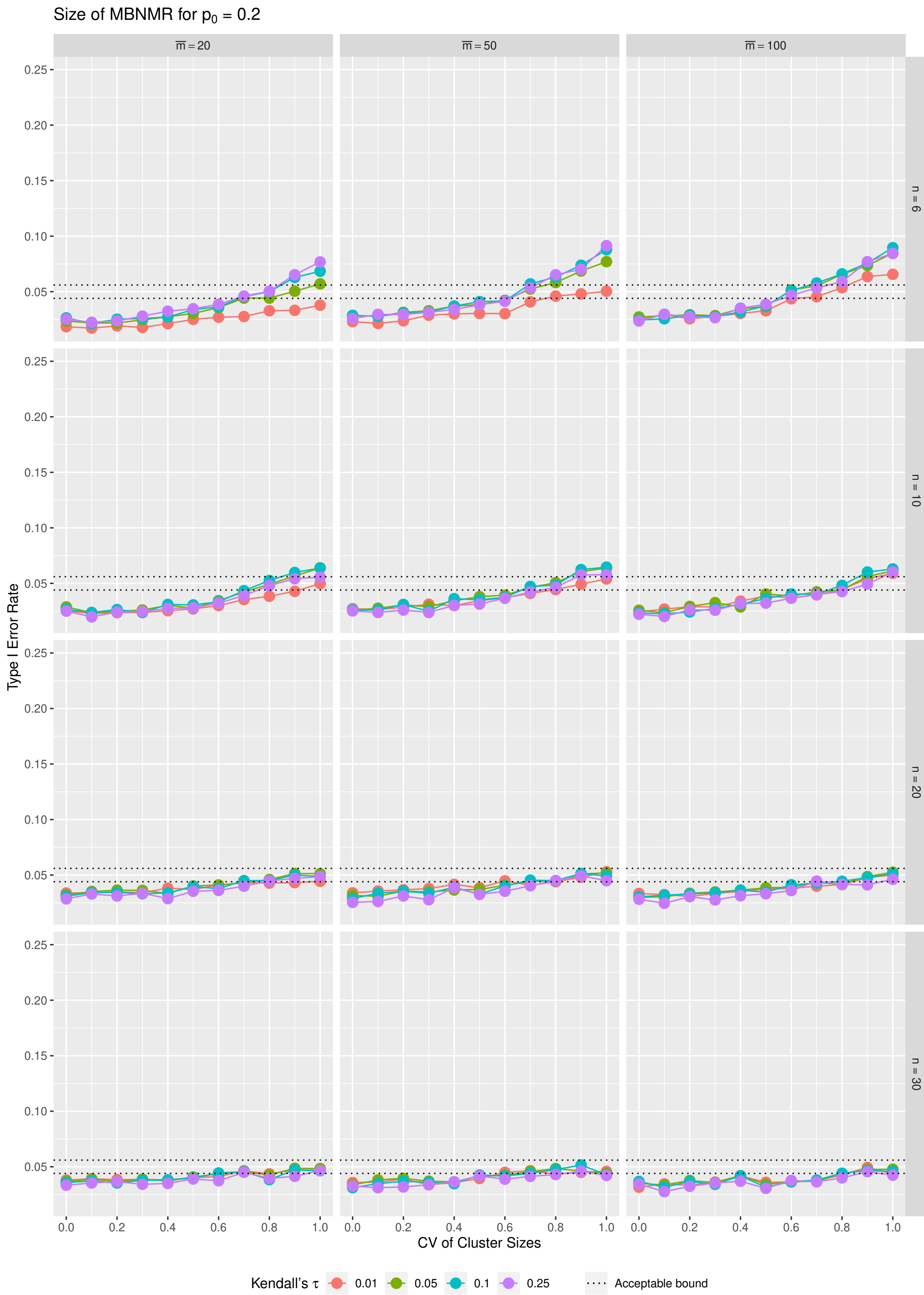
Web Figure 17: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the KCMR bias-corrected sandwich variance estimator.



Web Figure 18: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the FGMR bias-corrected sandwich variance estimator.



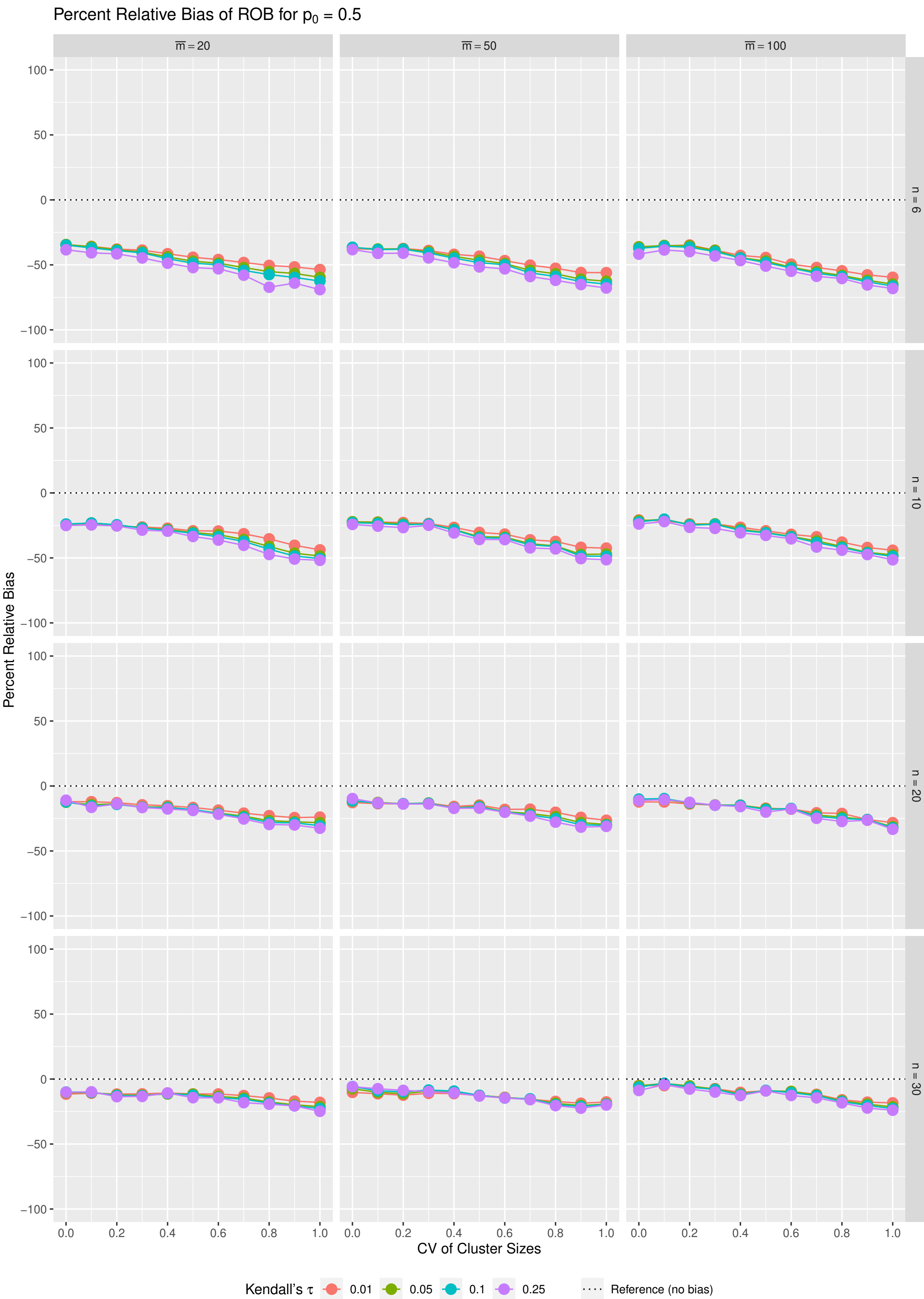
Web Figure 19: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the MDMR bias-corrected sandwich variance estimator.



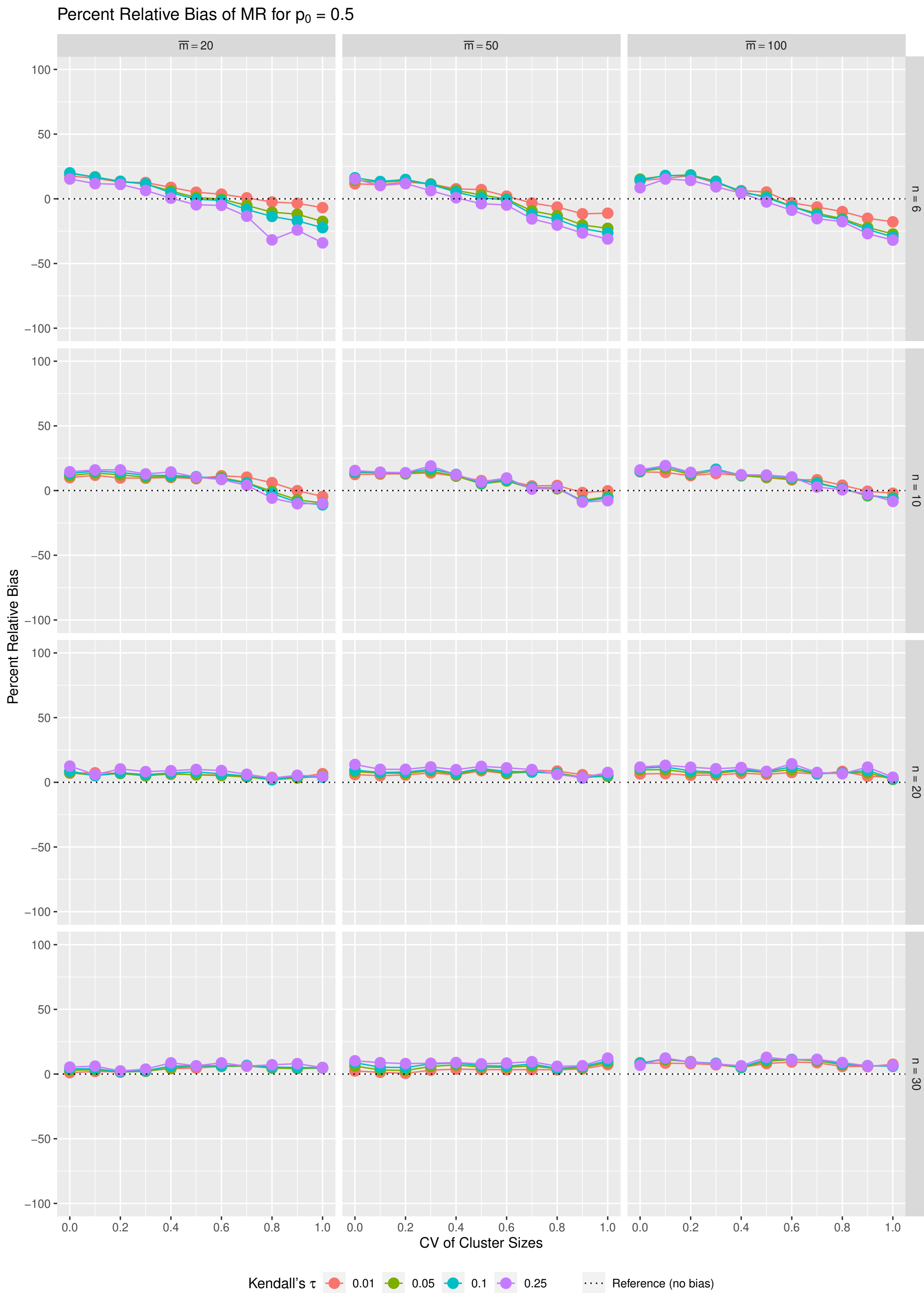
Web Figure 20: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ under the marginal Cox model, based on the MBNMR bias-corrected sandwich variance estimator.

Web Appendix D: Web figures from the main simulation study for $p_0 = 0.5$

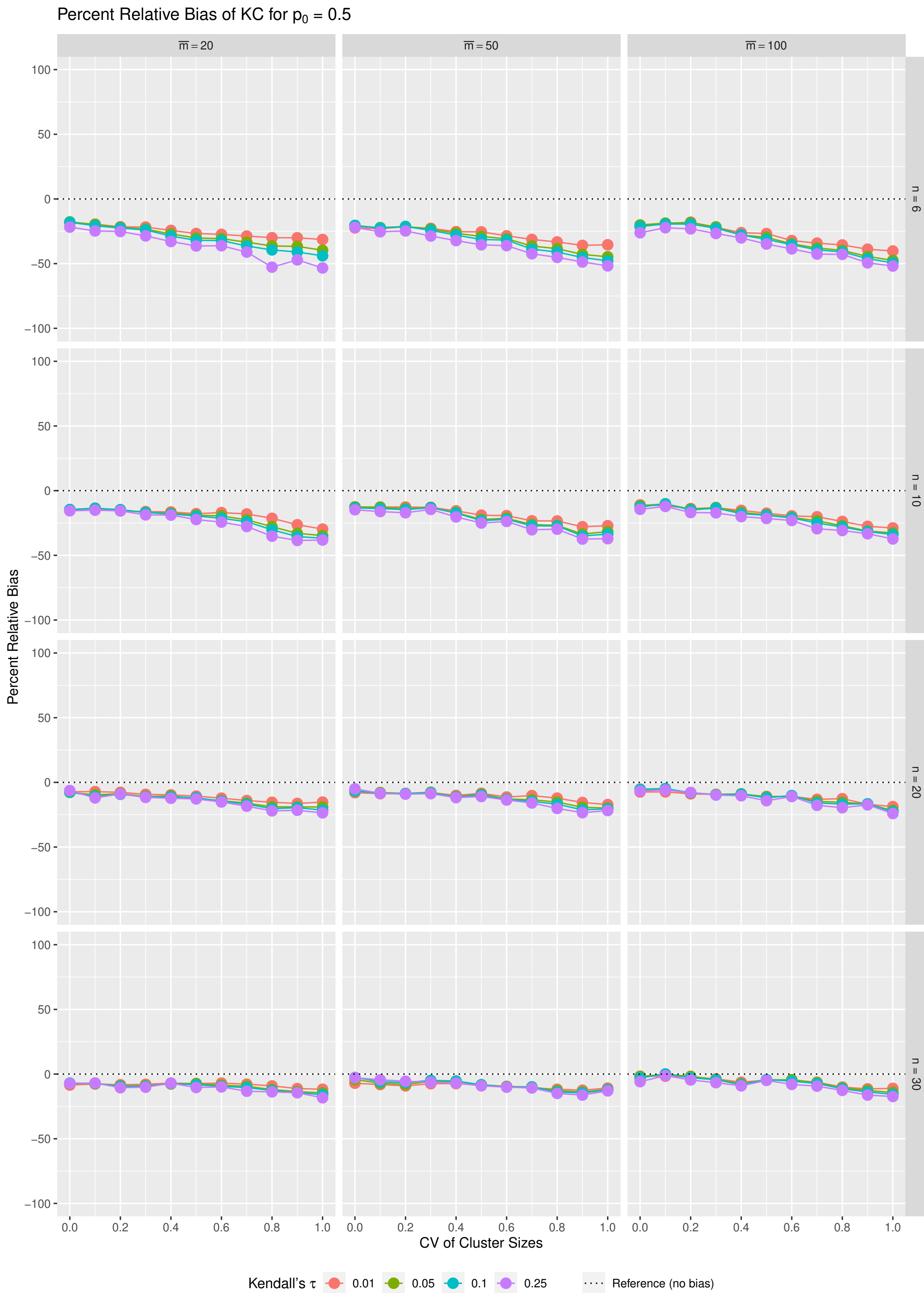
- Web Figures 21-30 present the results for the percent relative bias of different variance estimators for $p_0 = 0.5$.
  - Web Figure 21 (Page 28) refers to the ROB variance estimator.
  - Web Figure 22 (Page 29) refers to the MR variance estimator.
  - Web Figures 23, 24, 25, and 26 (Page 30-33) refer to the KC, FG, MD, and MBN variance estimators, respectively.
  - Web Figures 27, 28, 29, and 30 (Page 34-37) refer to the KCMR, FGMR, MDMR, and MBNMR variance estimators, respectively.
- Web Figures 31-40 present the results for empirical type I error rates based on different variance estimators for $p_0 = 0.5$.
  - Web Figure 31 (Page 38) refers to the ROB variance estimator.
  - Web Figure 32 (Page 39) refers to the MR variance estimator.
  - Web Figures 33, 34, 35, and 36 (Page 40-43) refer to the KC, FG, MD, and MBN variance estimators, respectively.
  - Web Figures 37, 38, 39, and 40 (Page 44-47) refer to the KCMR, FGMR, MDMR, and MBNMR variance estimators, respectively.



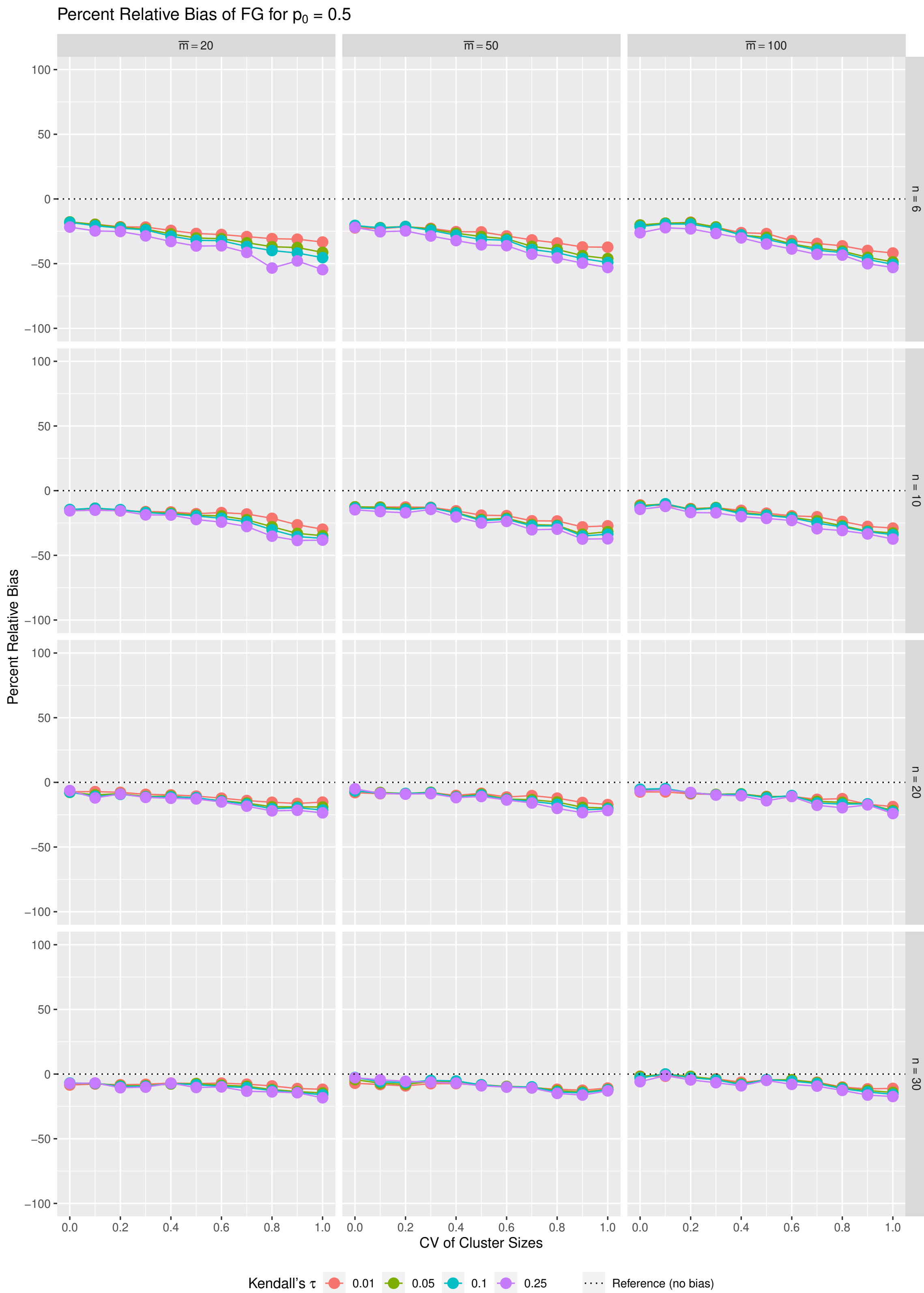
Web Figure 21: Percent relative bias of the uncorrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



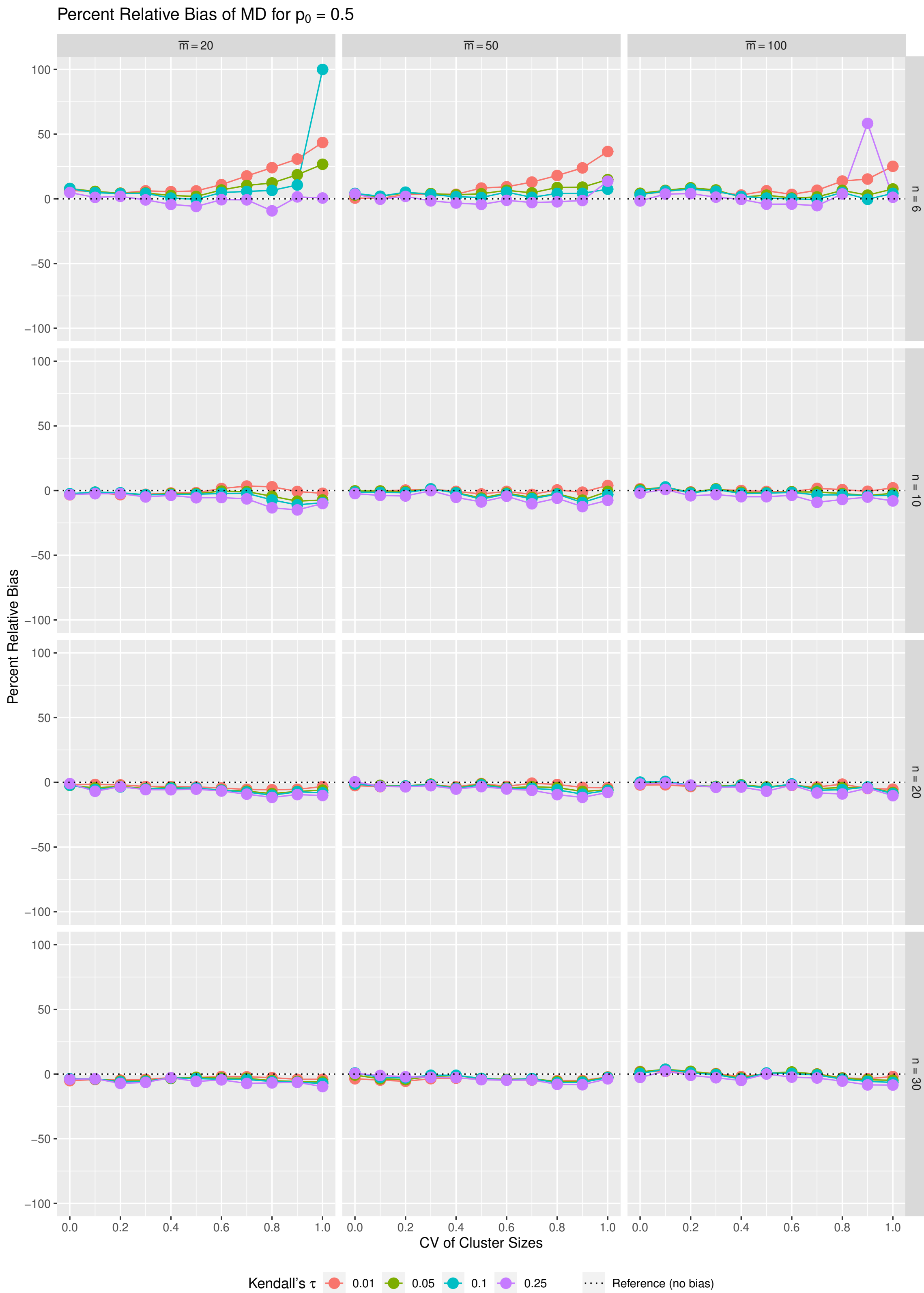
Web Figure 22: Percent relative bias of the martingale residual-based bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



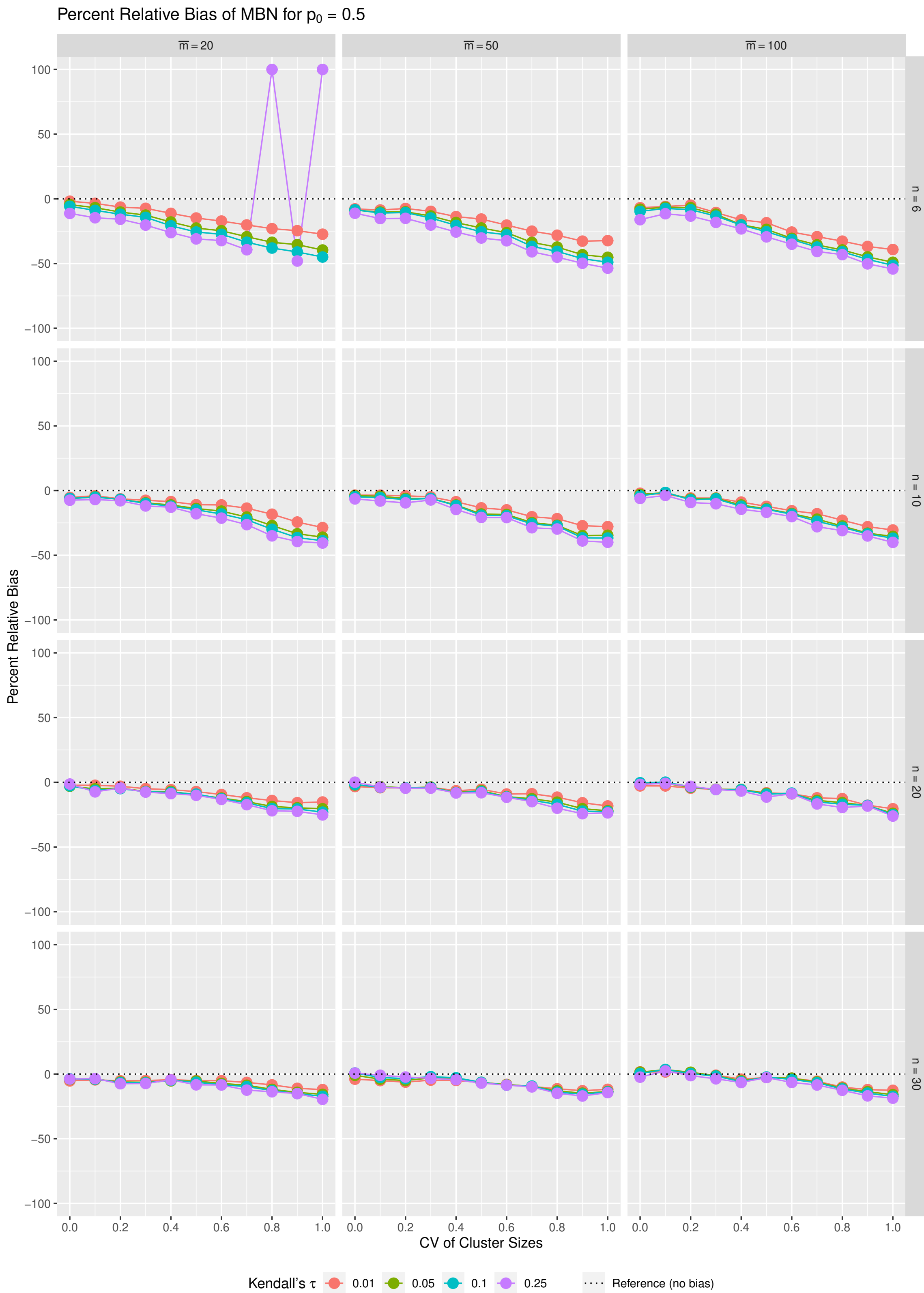
Web Figure 23: Percent relative bias of the KC bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



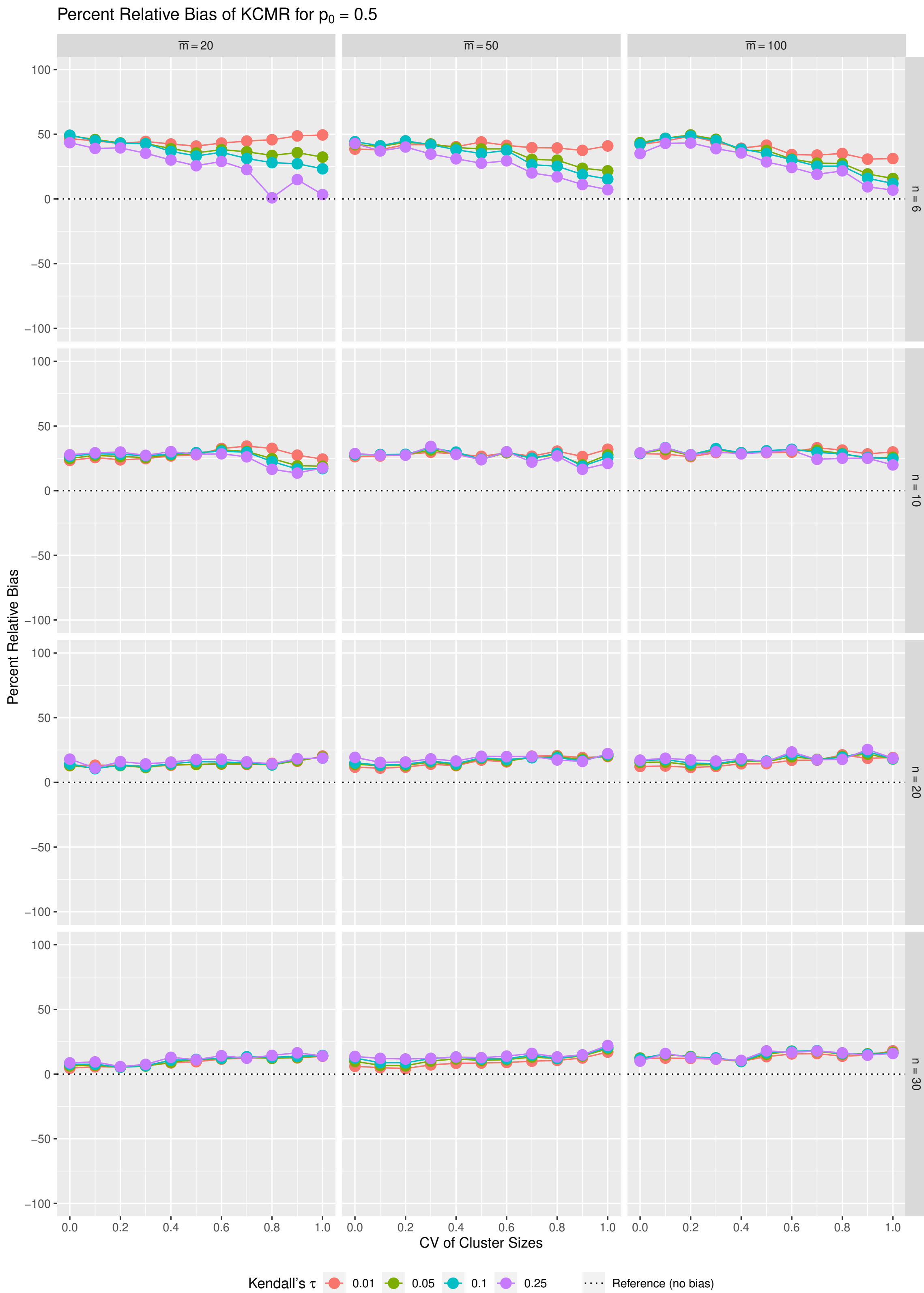
Web Figure 24: Percent relative bias of the FG bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



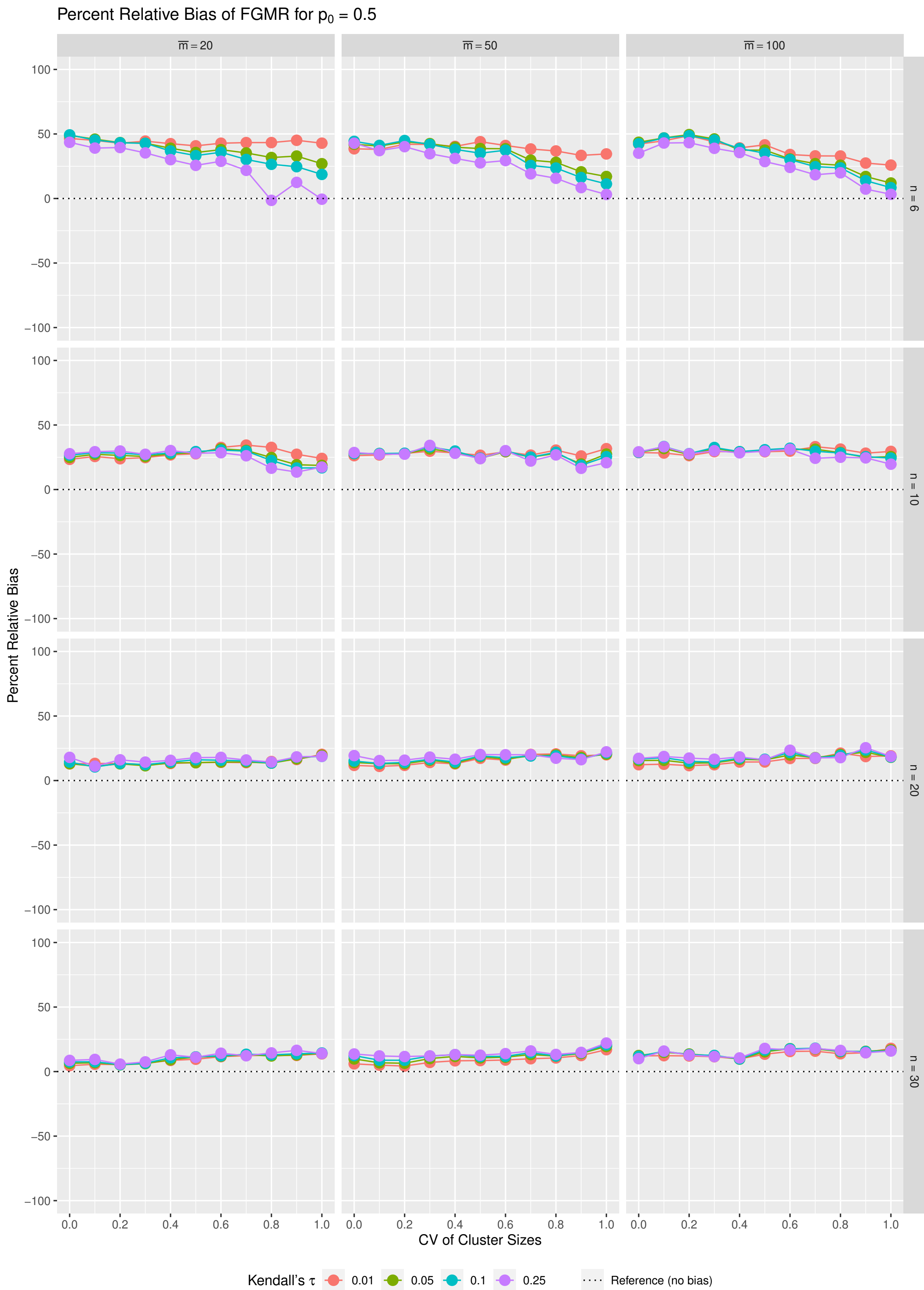
Web Figure 25: Percent relative bias of the MD bias-corrected sandwich estimator, for $p_0 = 0.5$ under the marginal Cox model. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



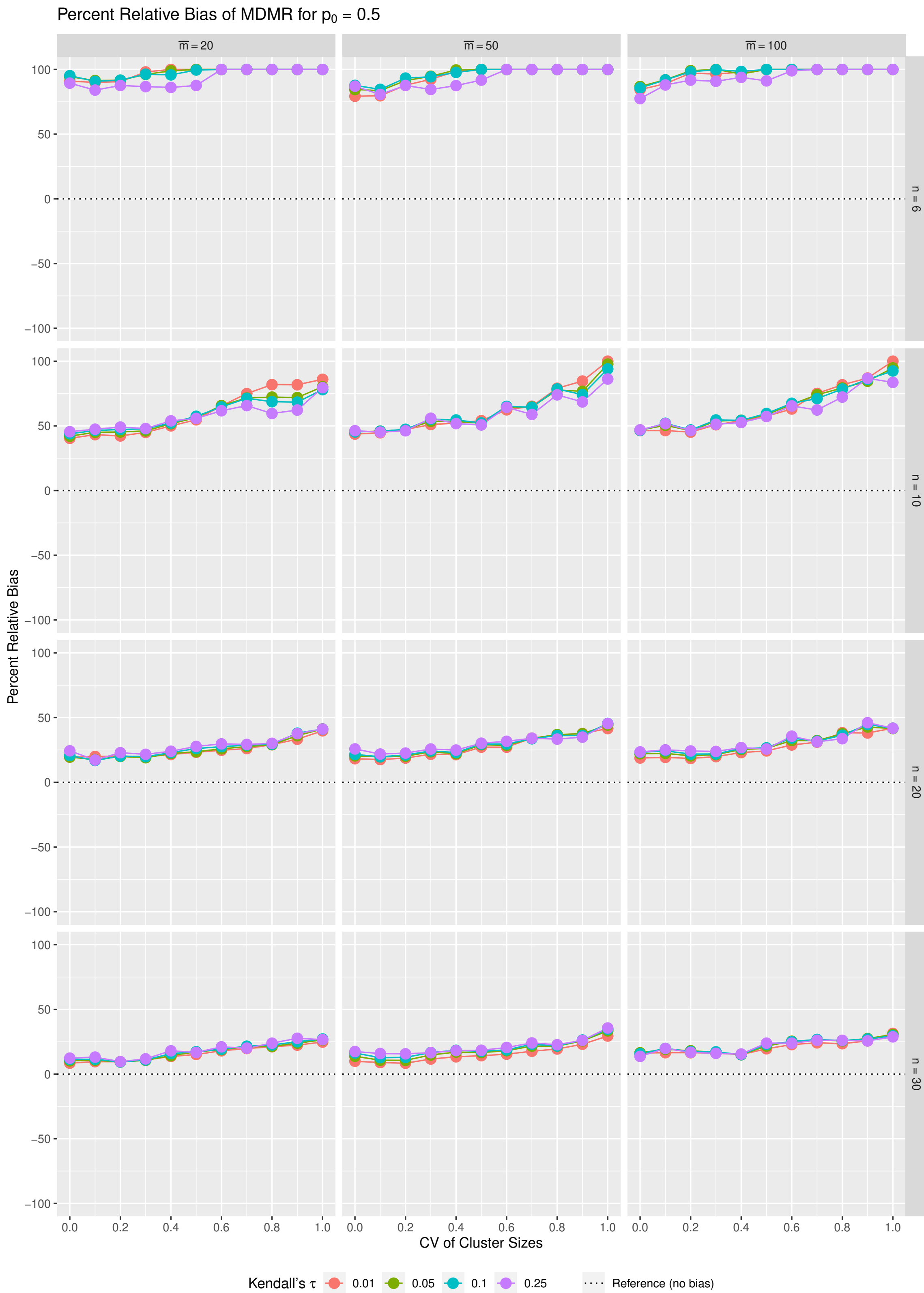
Web Figure 26: Percent relative bias of the MBN bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



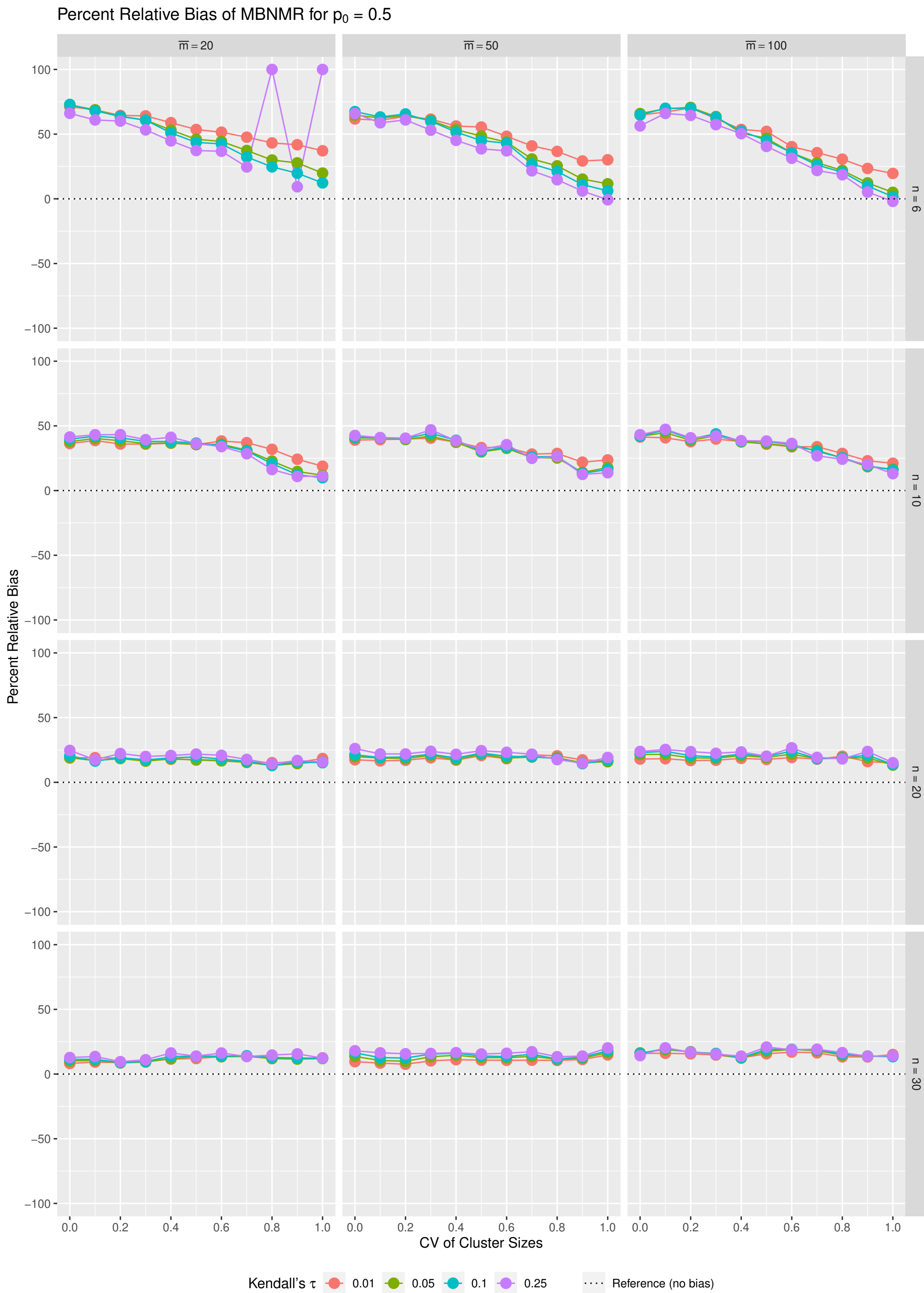
Web Figure 27: Percent relative bias of the KCMR bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



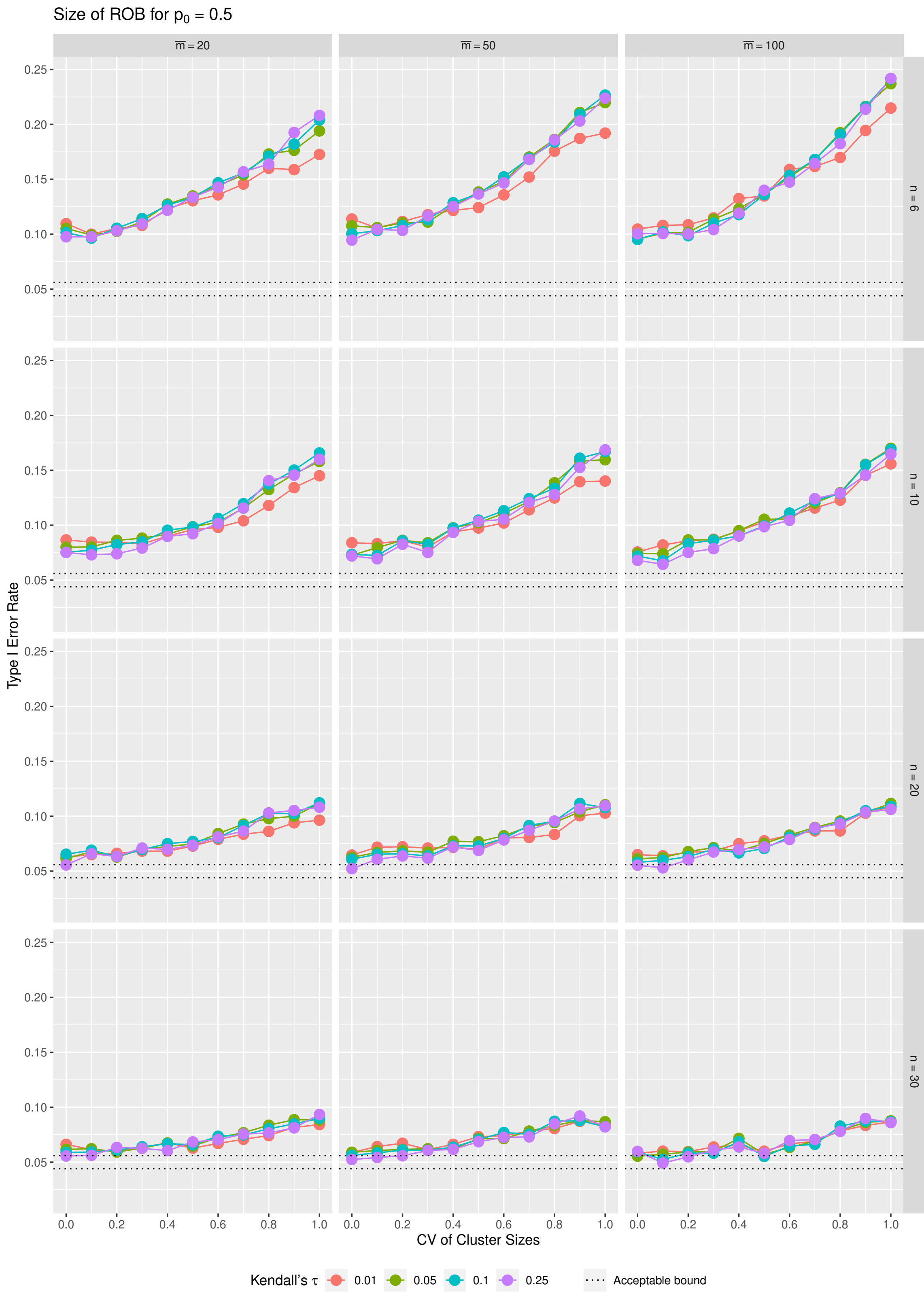
Web Figure 28: Percent relative bias of the FGMR bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model.



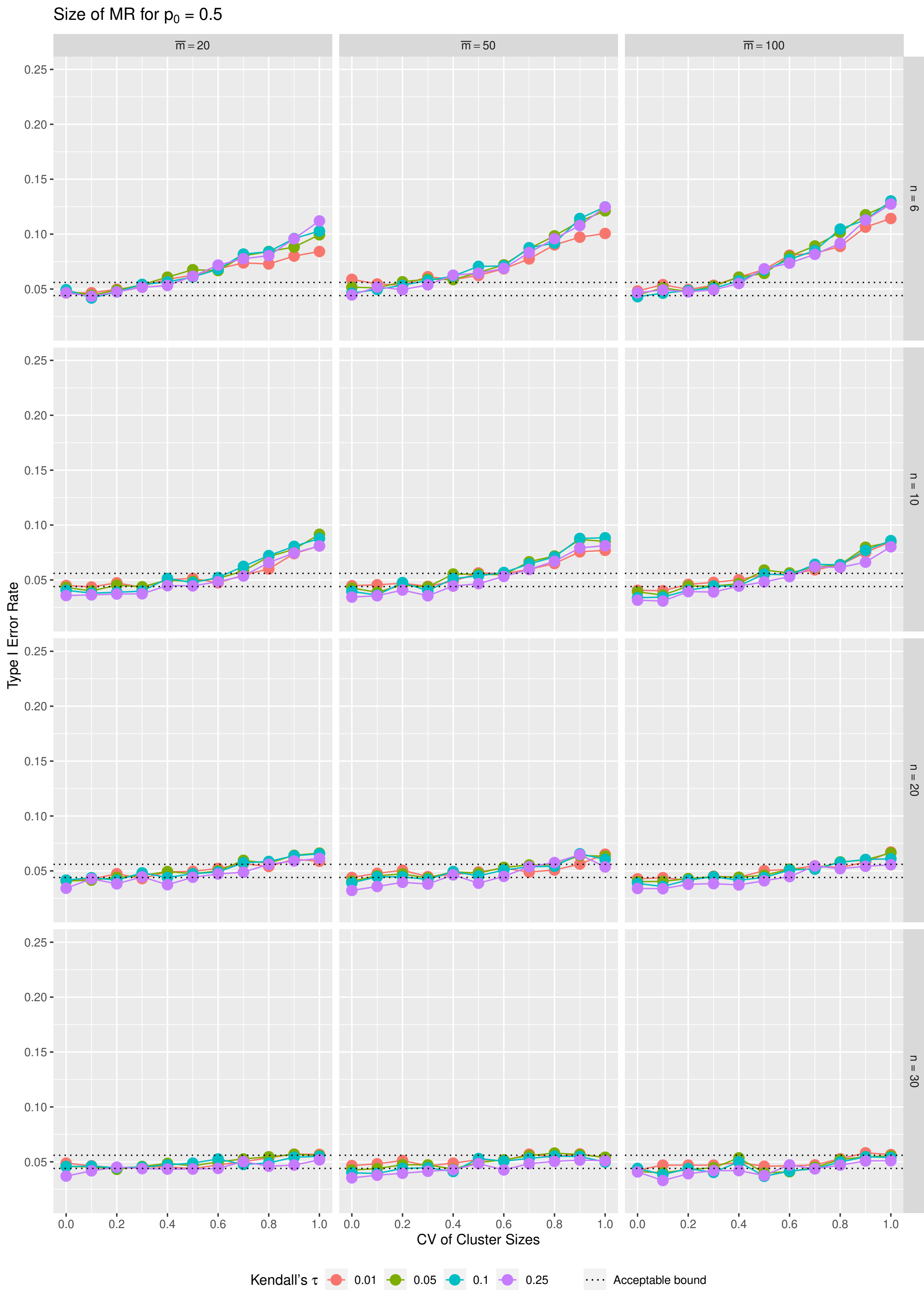
Web Figure 29: Percent relative bias of the MDMR bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



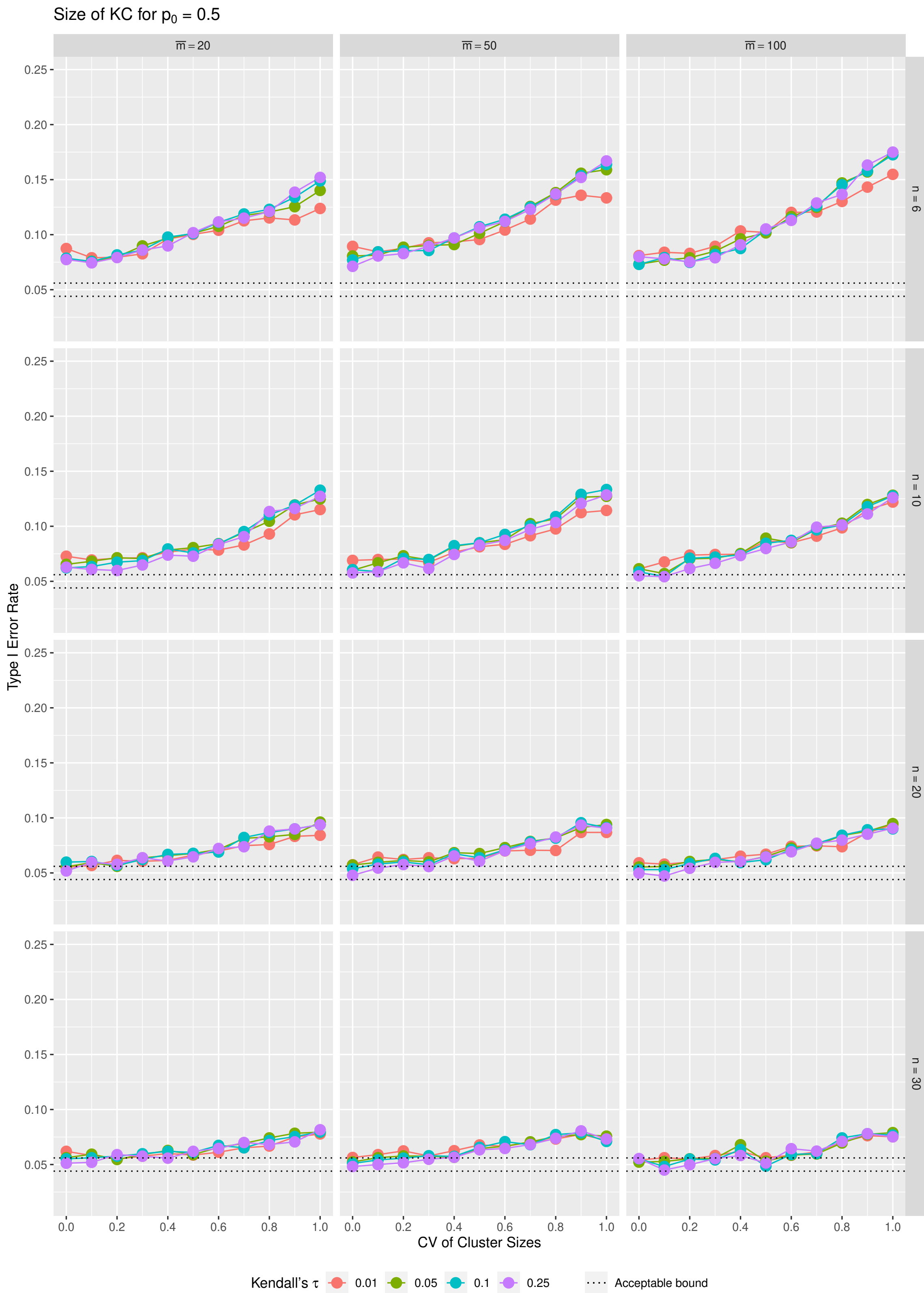
Web Figure 30: Percent relative bias of the MBNMR bias-corrected sandwich variance estimator, for $p_0 = 0.5$ under the marginal Cox model. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



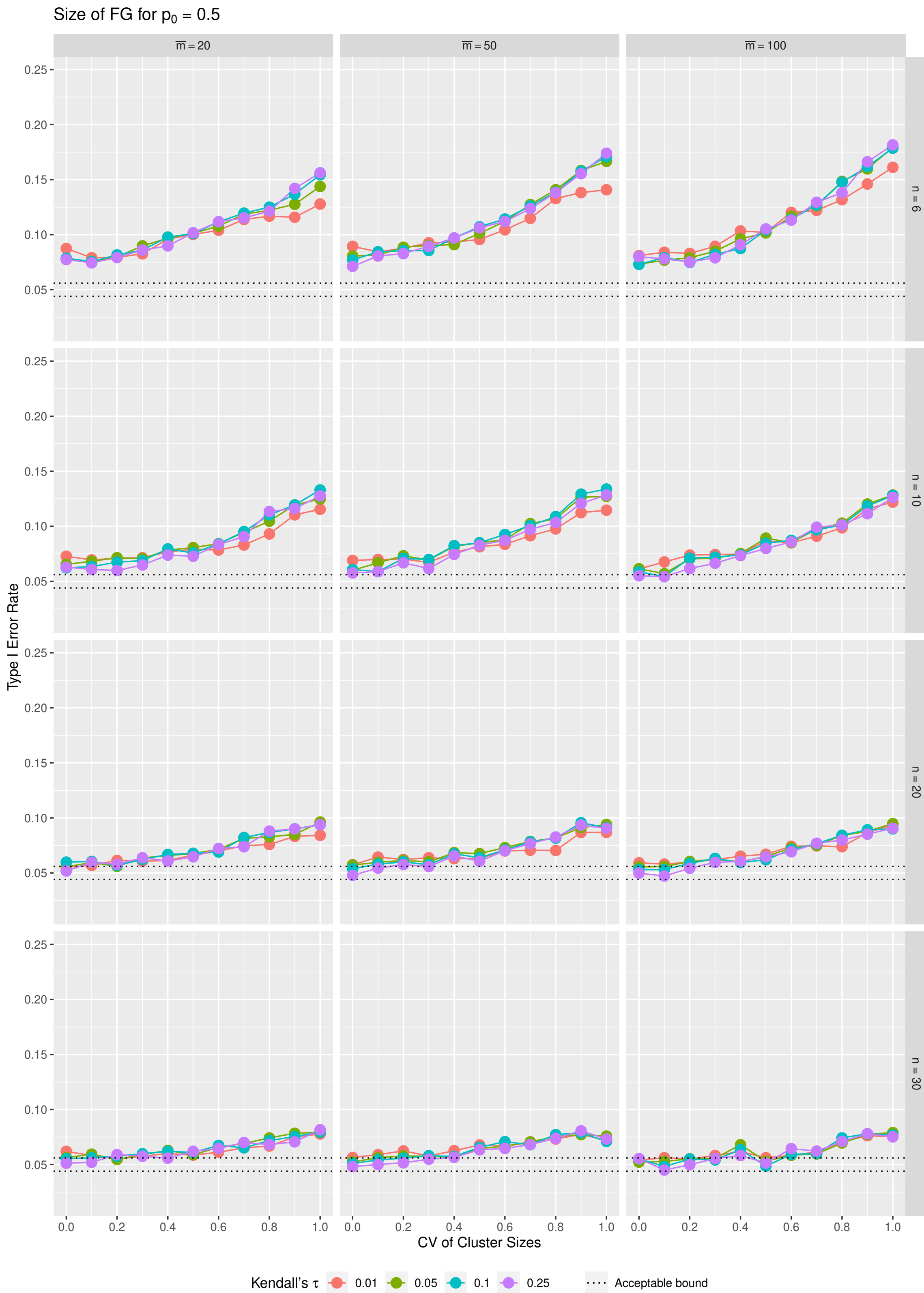
Web Figure 31: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the uncorrected sandwich variance estimator.



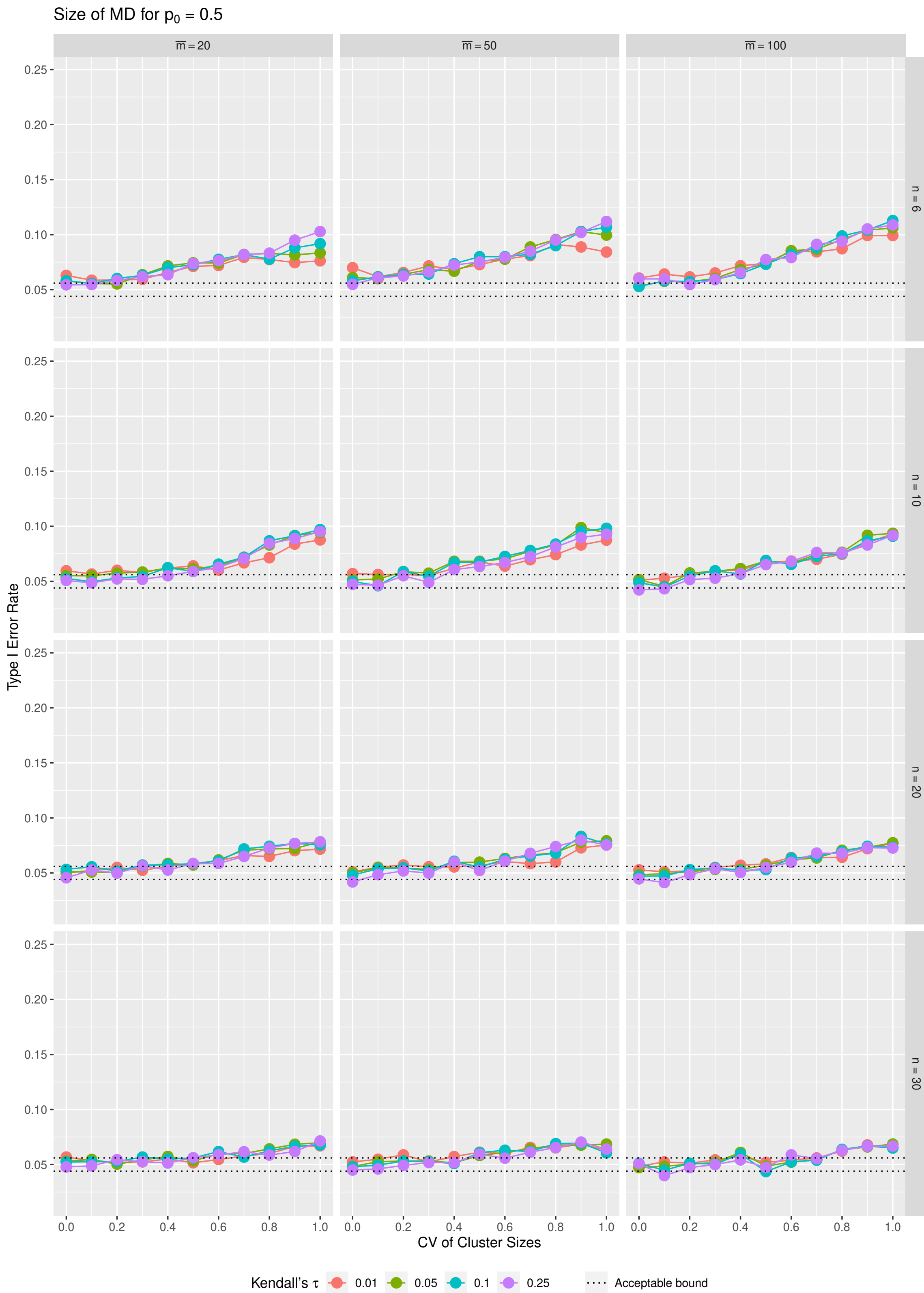
Web Figure 32: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the martingale residual-based bias-corrected sandwich variance estimator.



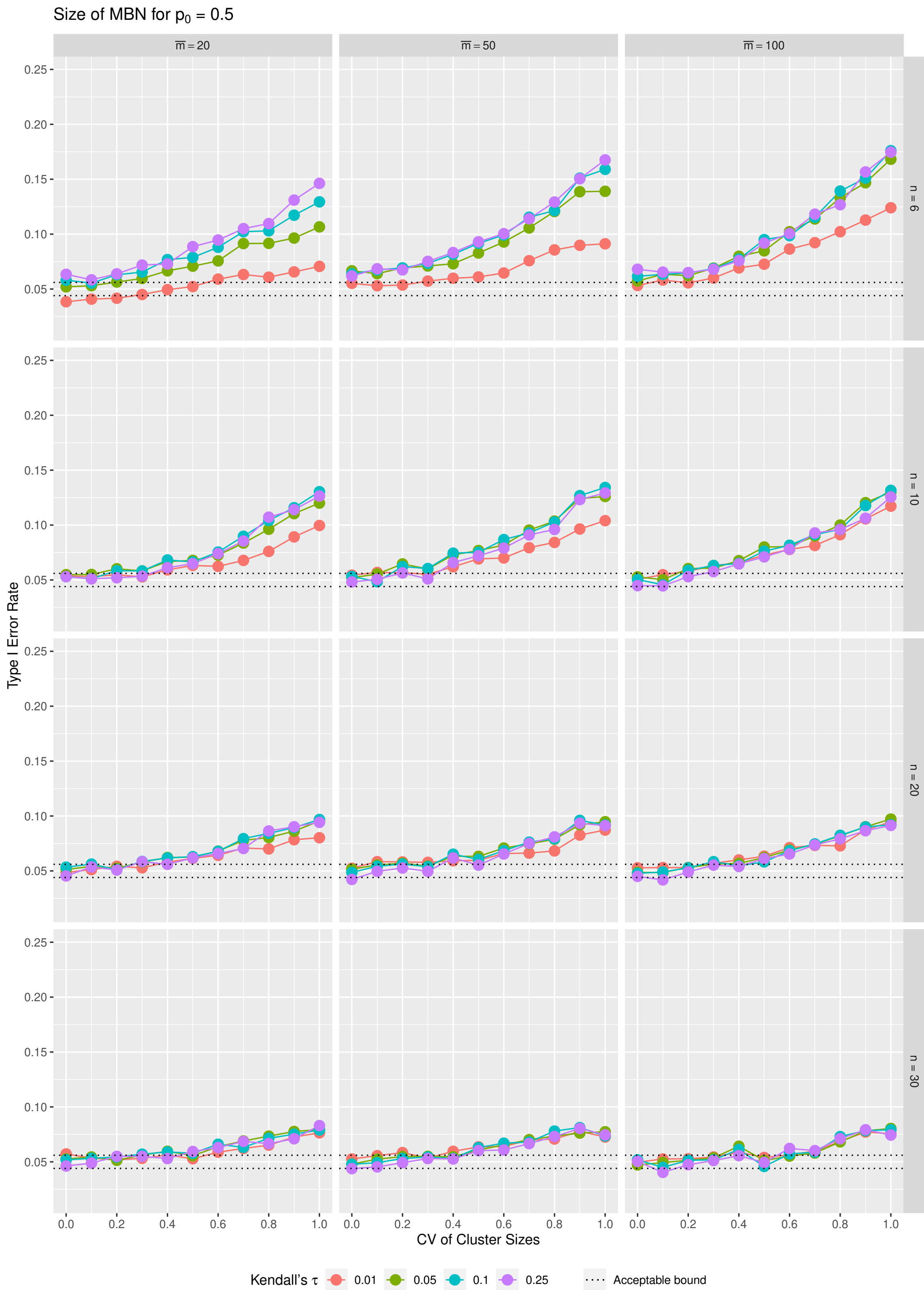
Web Figure 33: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the KC bias-corrected sandwich variance estimator.



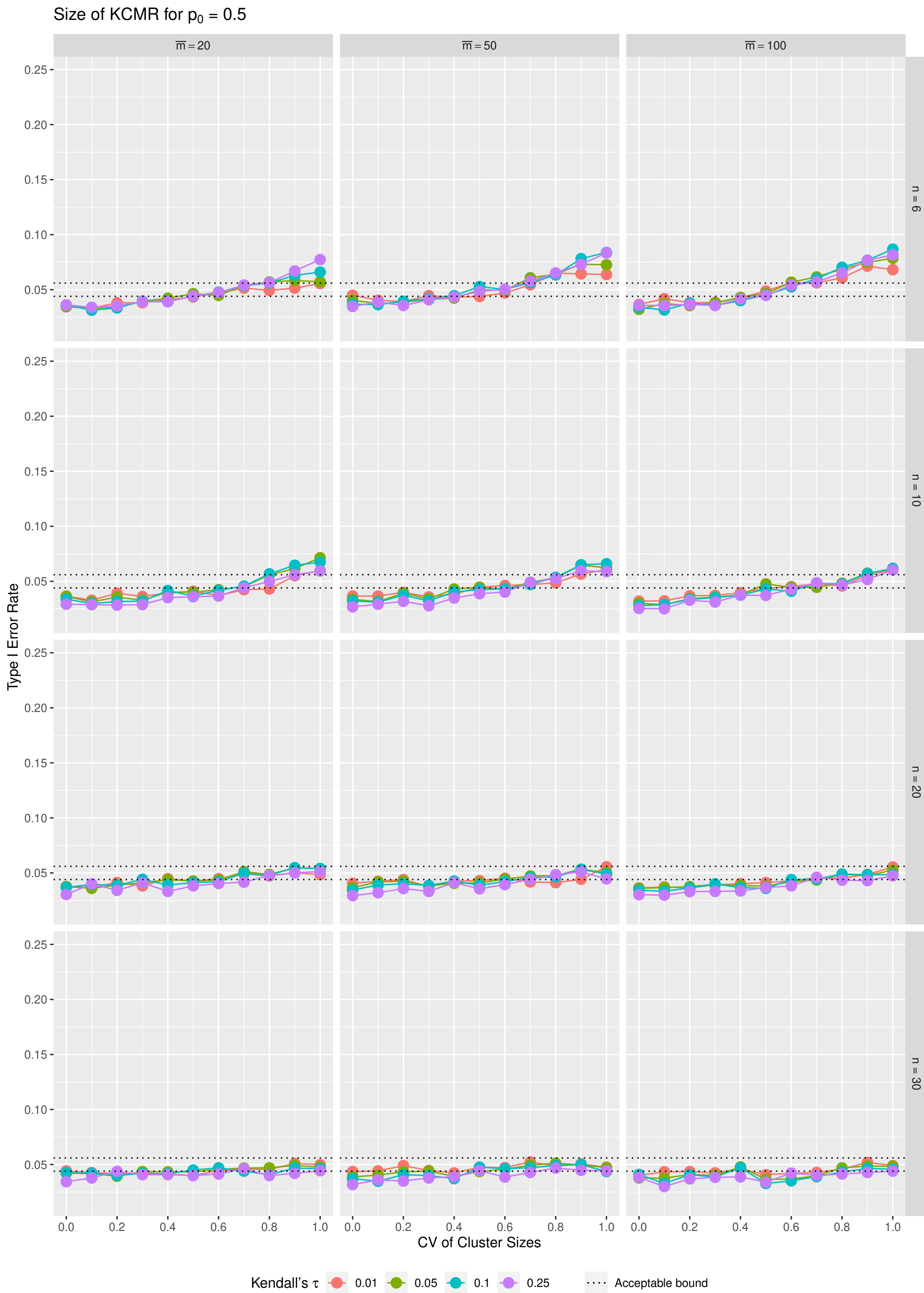
Web Figure 34: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the FG bias-corrected sandwich variance estimator.



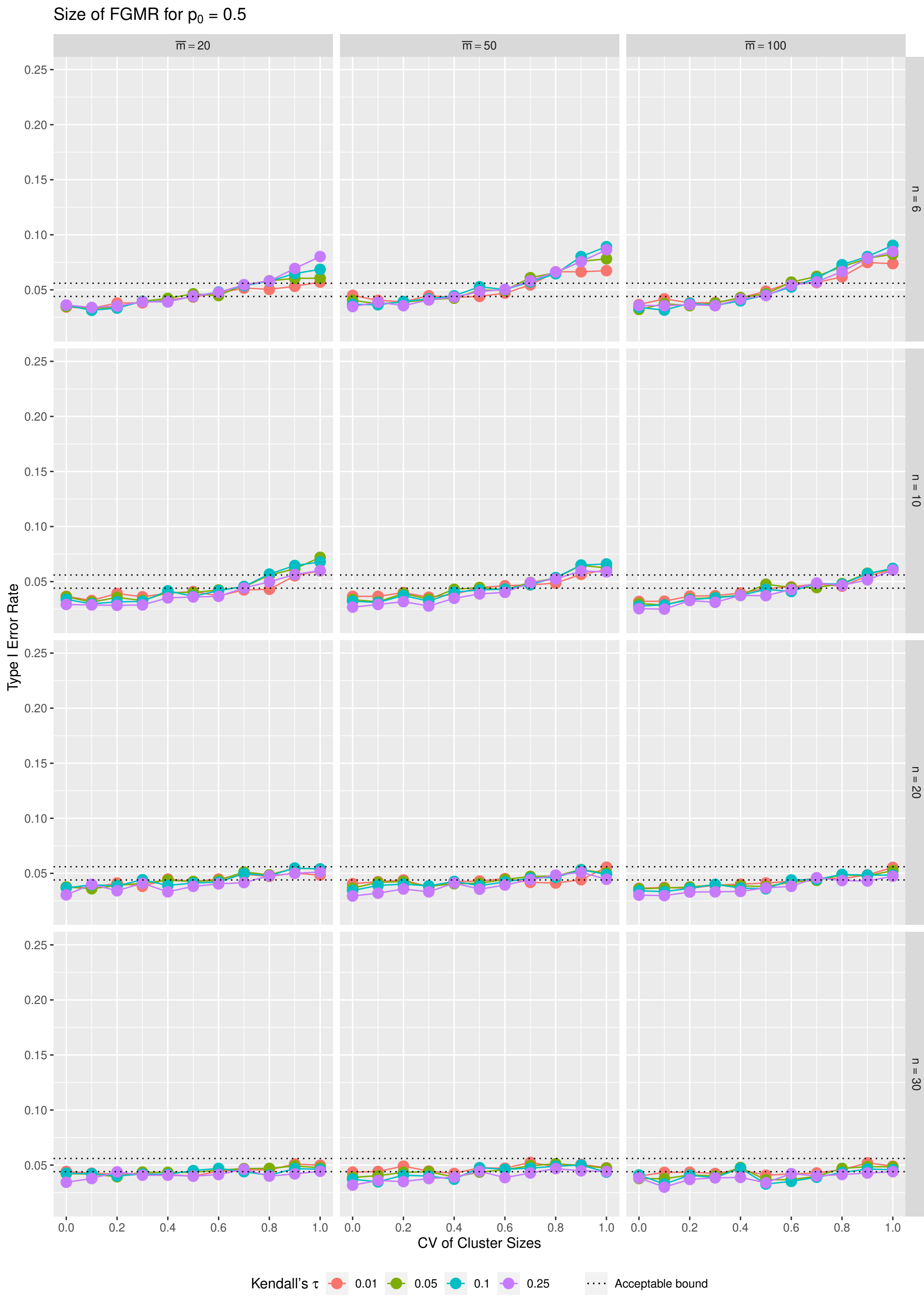
Web Figure 35: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the MD bias-corrected sandwich estimator.



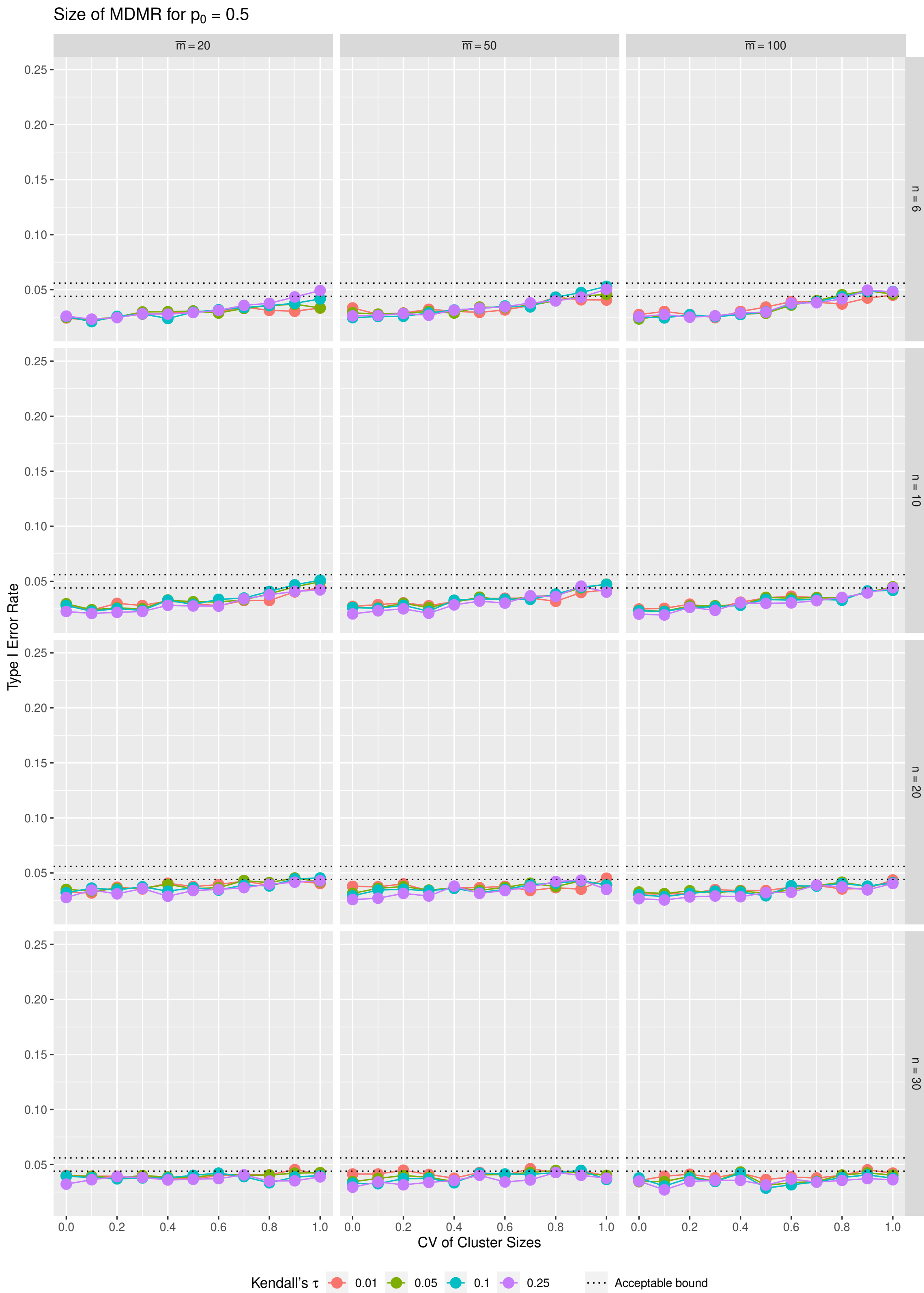
Web Figure 36: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the MBN bias-corrected sandwich variance estimator.



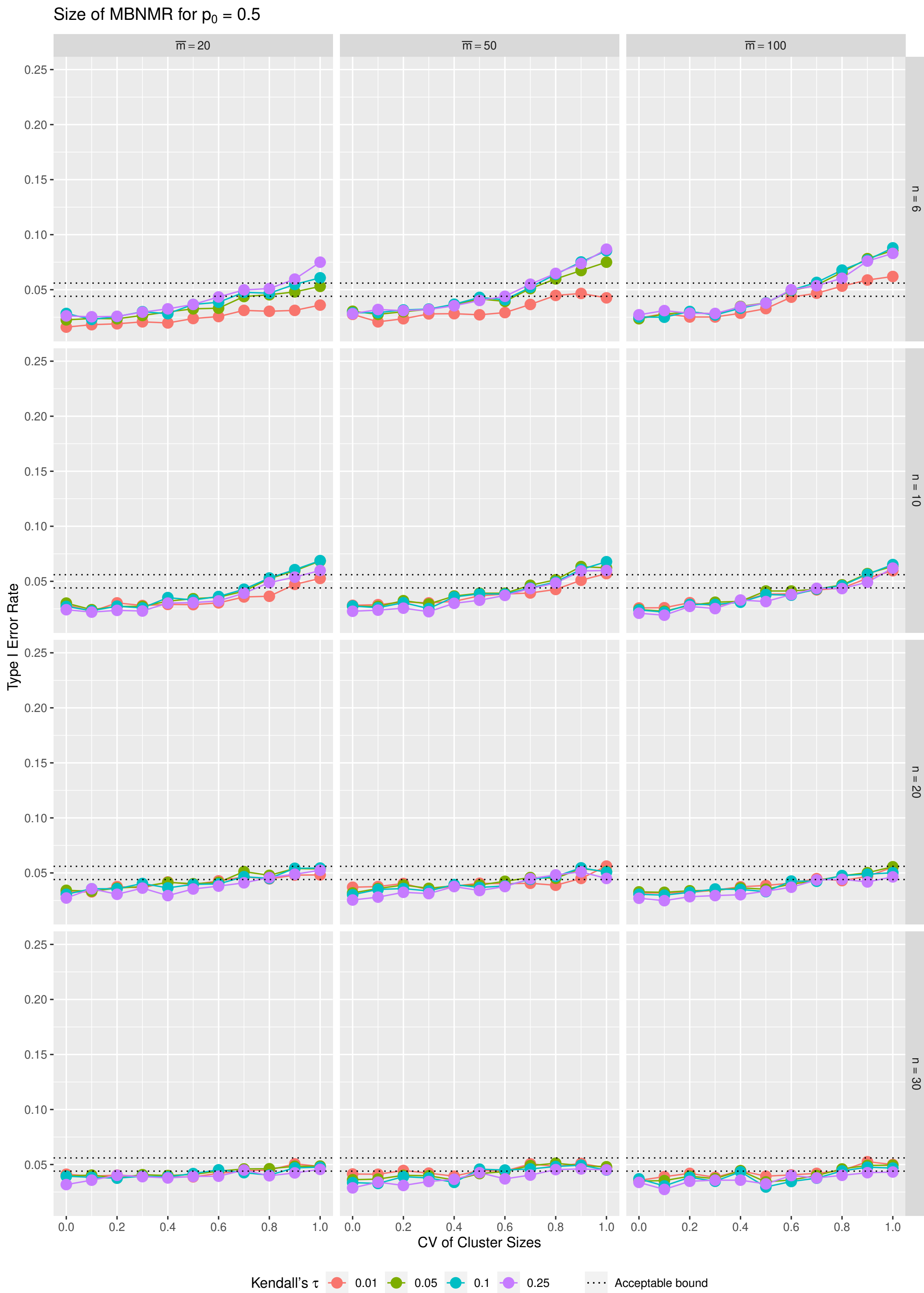
Web Figure 37: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the KCMR bias-corrected sandwich variance estimator.



Web Figure 38: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the FGMR bias-corrected sandwich variance estimator.



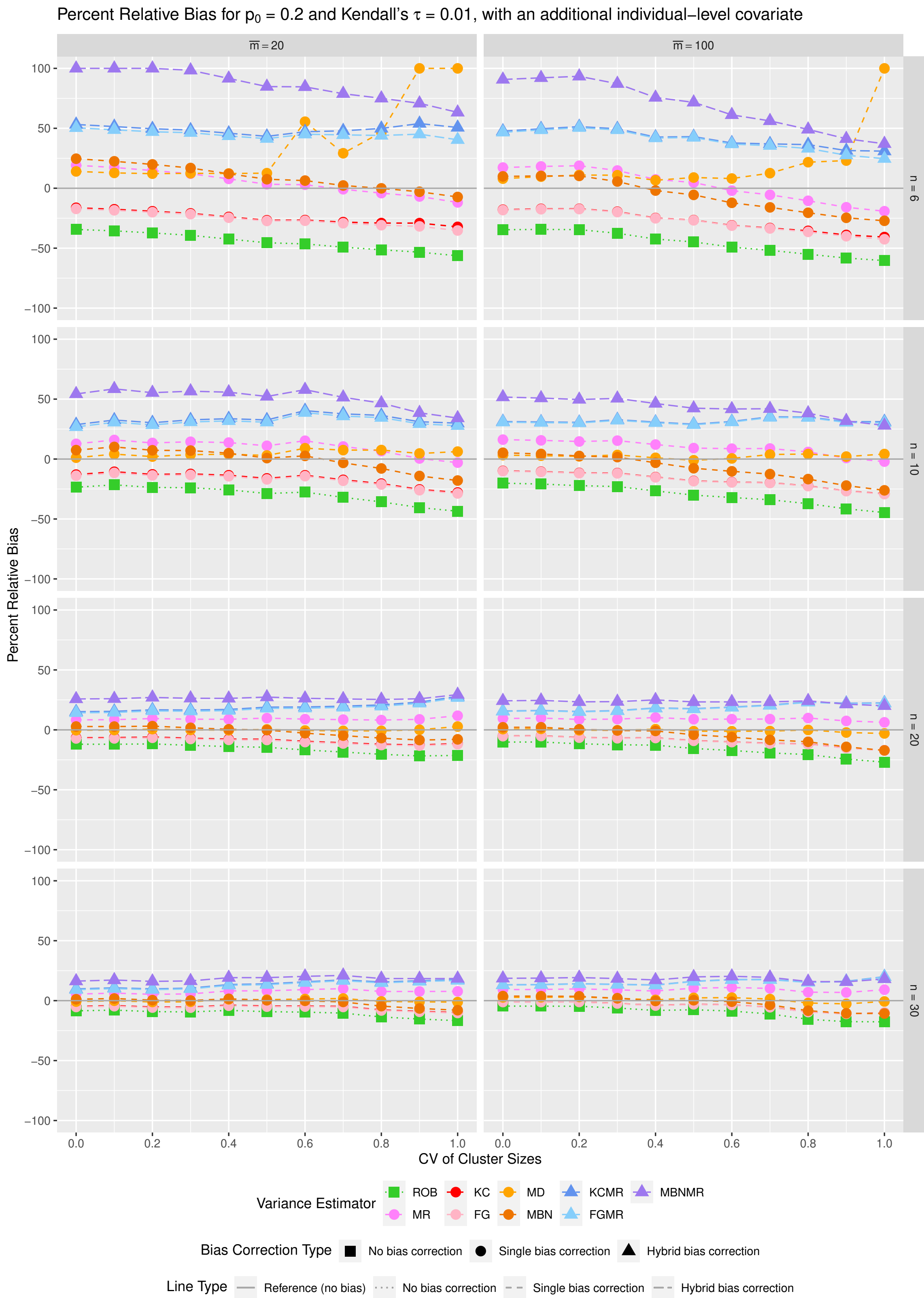
Web Figure 39: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the MDMR bias-corrected sandwich variance estimator.



Web Figure 40: Empirical type I error rates of intervention effect tests for $p_0 = 0.5$ under the marginal Cox model, based on the MBNMR bias-corrected sandwich variance estimator.

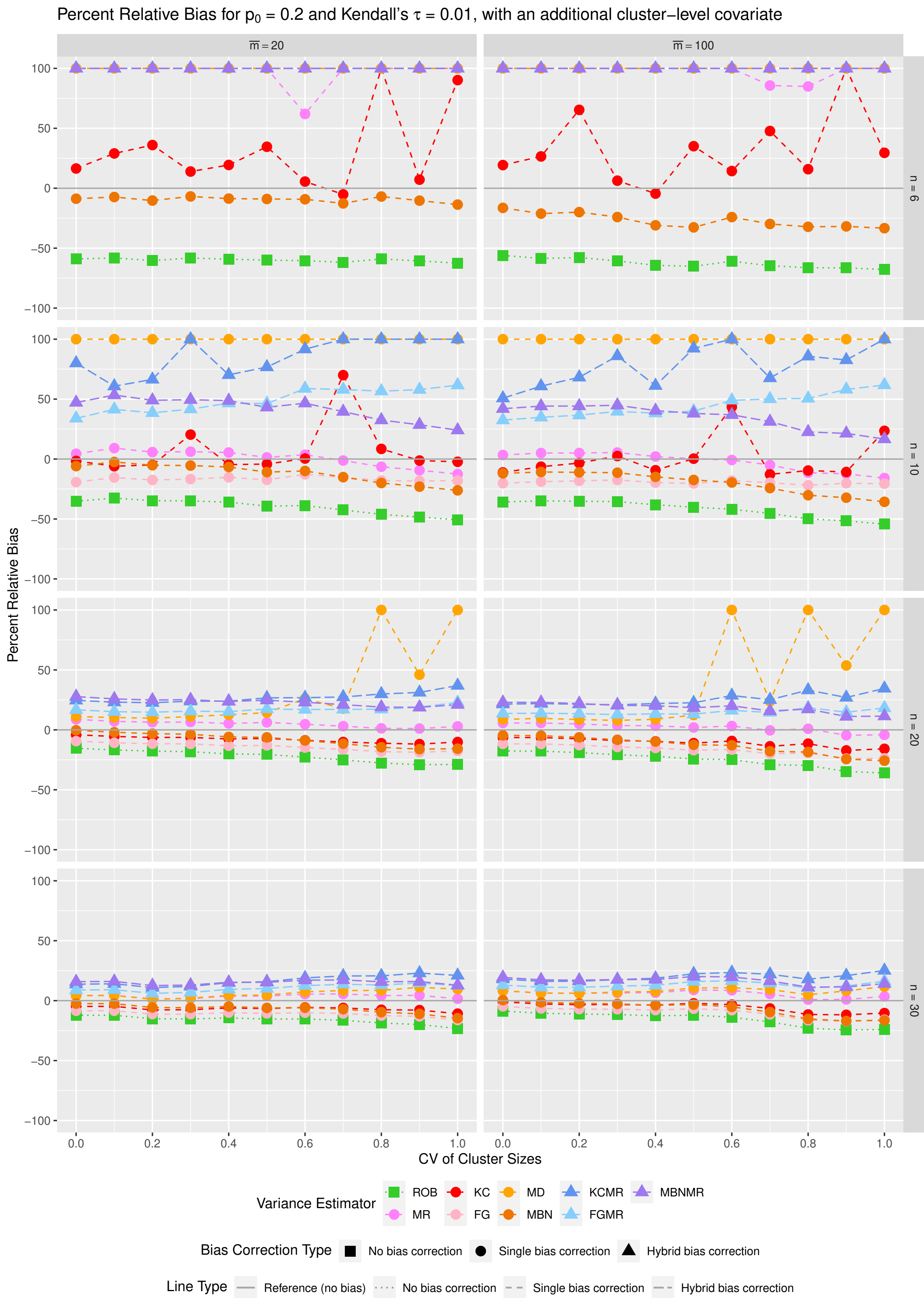
Web Appendix E: Web figures from the additional simulation study for $p_0 = 0.2$

- Web Figures 41-44 present the results of different variance estimators with an additional covariate.
  - Web Figure 41 (Page 49) refers to the percent relative bias with an additional individual-level covariate.
  - Web Figure 42 (Page 50) refers to empirical type I error rates with an additional individual-level covariate.
  - Web Figures 43 (Page 51) refers to the percent relative bias with an additional cluster-level covariate.
  - Web Figures 44 (Page 52) refers to empirical type I error rates with an additional cluster-level covariate.
- Web Figures 45-46 present the results of different variance estimators for larger CV of cluster sizes.
  - Web Figure 45 (Page 53) refers to the percent relative bias.
  - Web Figure 46 (Page 54) refers to empirical type I error rates.
- Web Figures 47 (Page 55) presents the results for empirical coverage probabilities of different variance estimators.

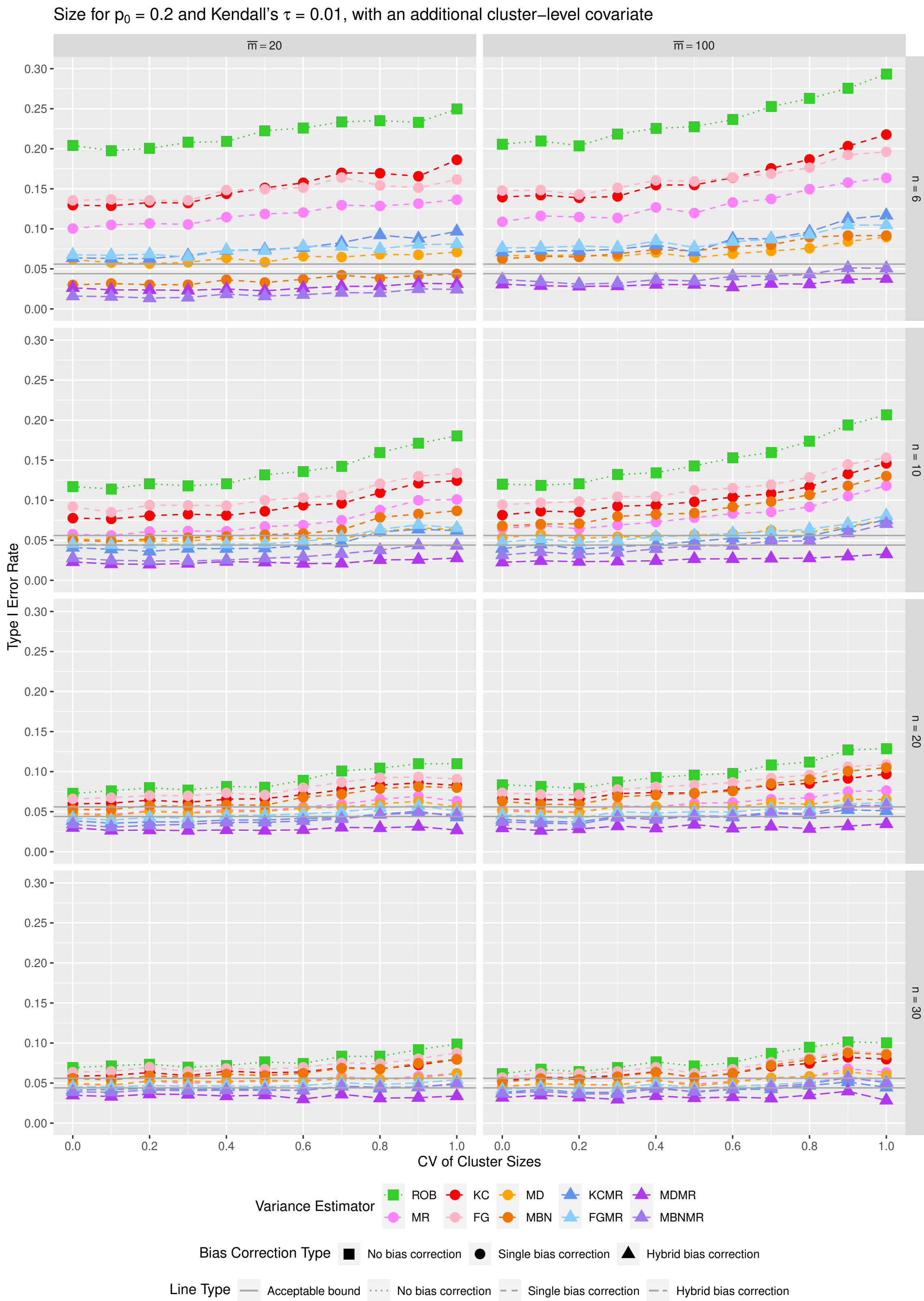


Web Figure 41: Percent relative bias of different variance estimators for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with an additional individual-level covariate. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.

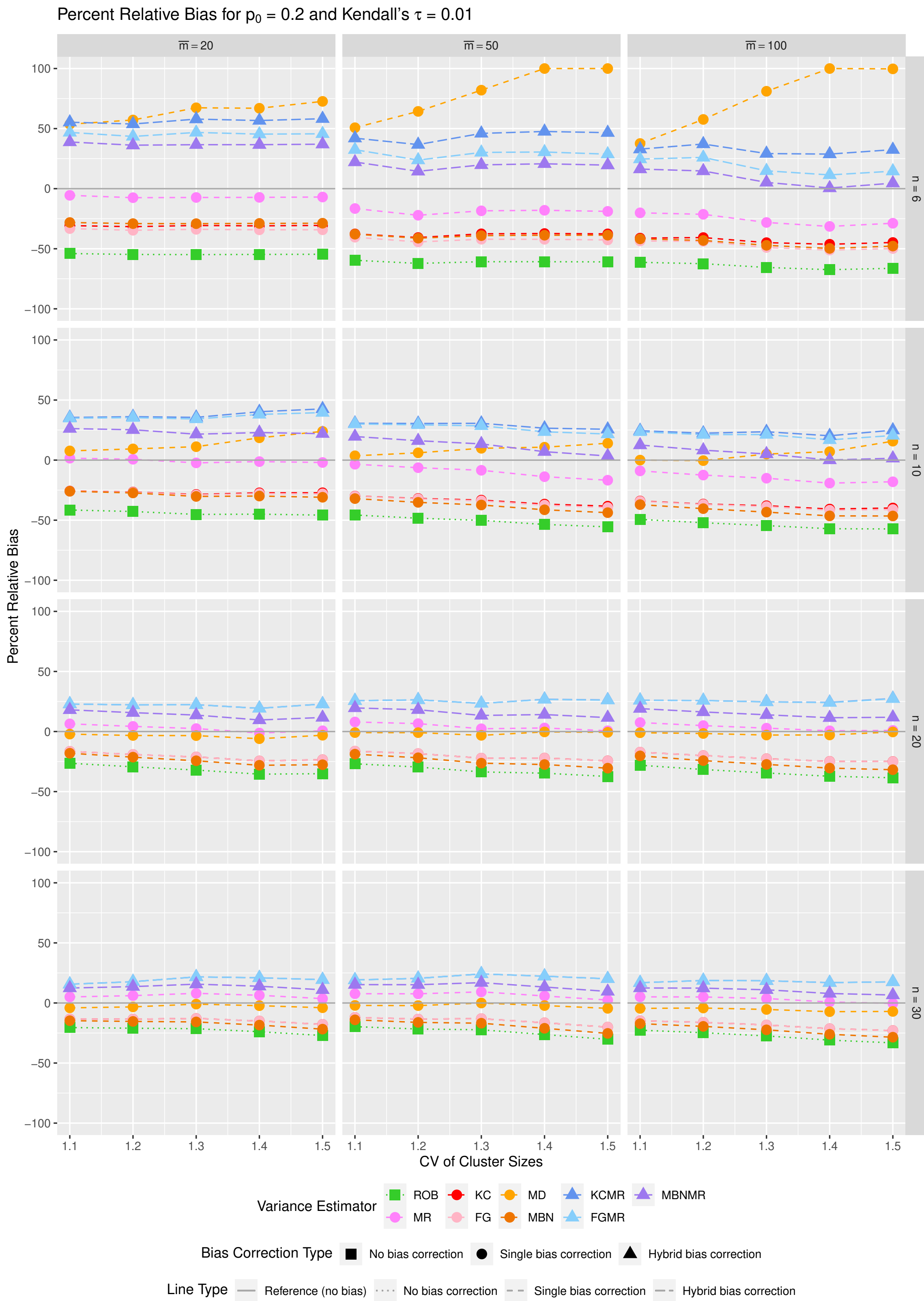
Web Figure 42: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with an additional individual-level covariate, based on different variance estimators.



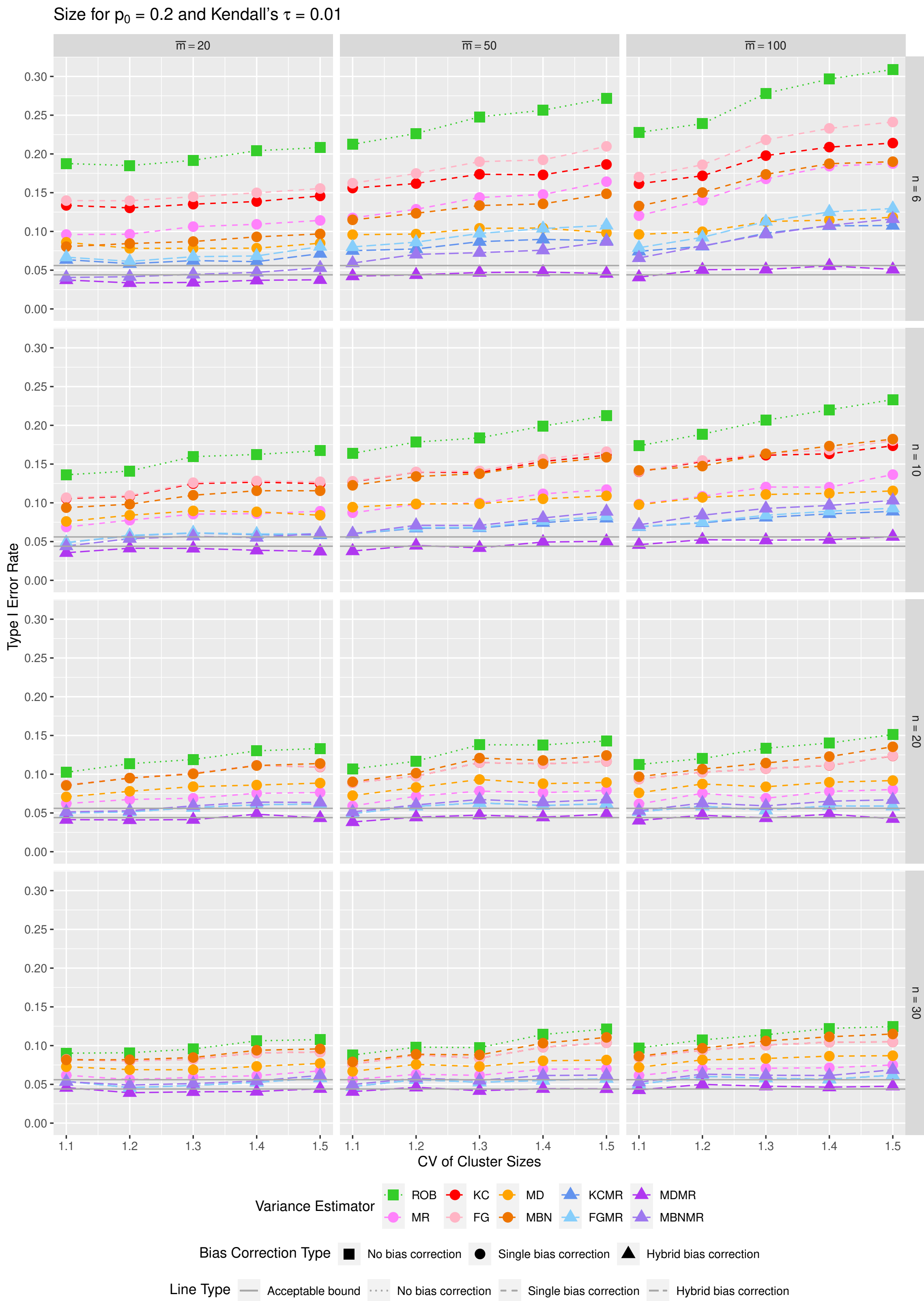
Web Figure 43: Percent relative bias of different variance estimators for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with an additional cluster-level covariate. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



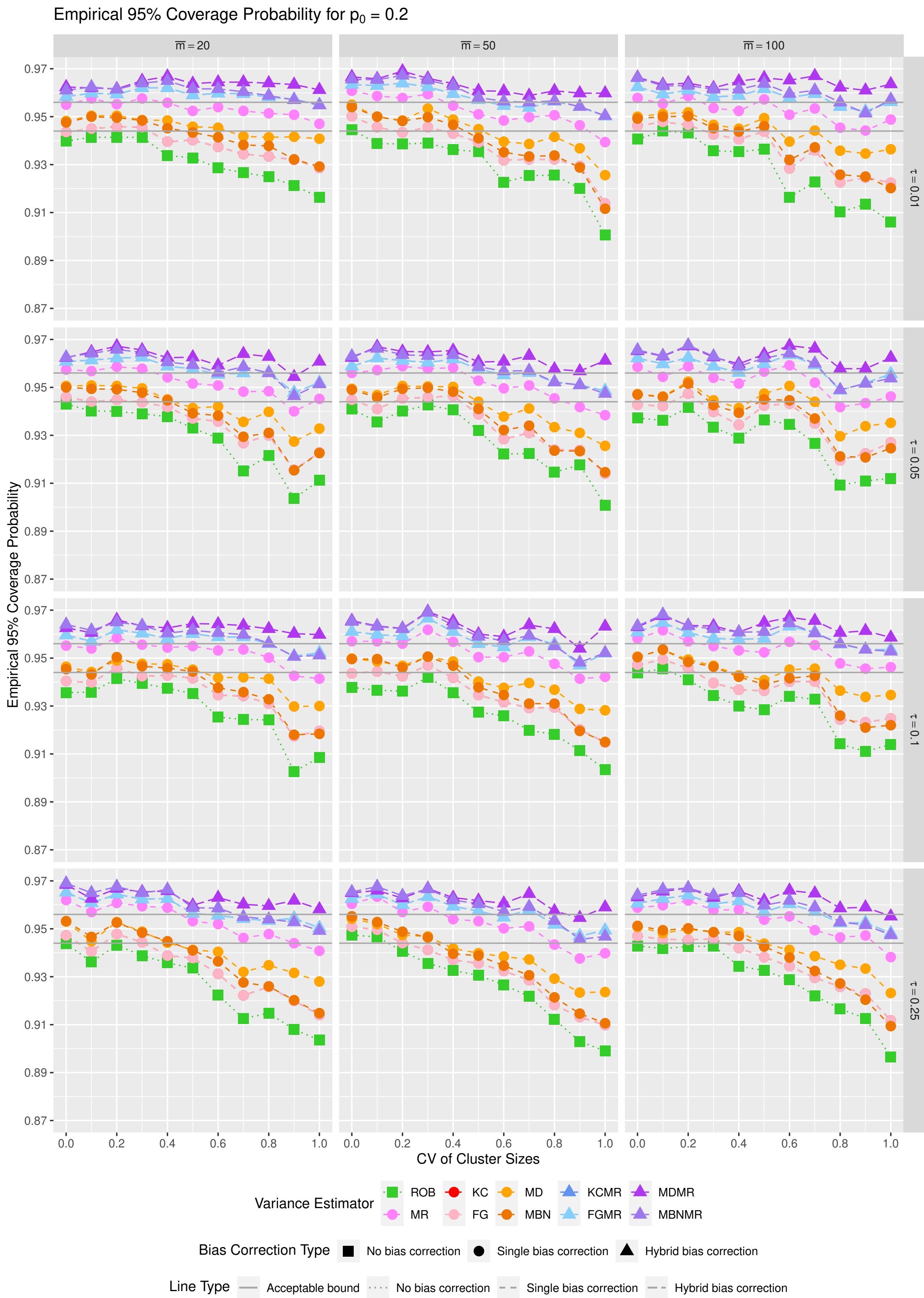
Web Figure 44: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with an additional cluster-level covariate, based on different variance estimators.



Web Figure 45: Percent relative bias of different variance estimators for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with larger CV of cluster sizes. For illustration purposes, the values of percent relative bias larger than 100 are plotted as 100.



Web Figure 46: Empirical type I error rates of intervention effect tests for $p_0 = 0.2$ and $\tau = 0.01$, under the marginal Cox model with larger CV of cluster sizes, based on different variance estimators.



Web Figure 47: Empirical coverage probabilities for the 95% confidence interval, for $p_0 = 0.2$ under the marginal Cox model, based on different variance estimators.

References

Spiekerman, C. F. and Lin, D. (1998). Marginal regression models for multivariate failure time data. *Journal of the American Statistical Association* **93,** 1164–1175.

Wei, L.-J., Lin, D. Y., and Weissfeld, L. (1989). Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *Journal of the American Statistical Association* **84,** 1065–1073.