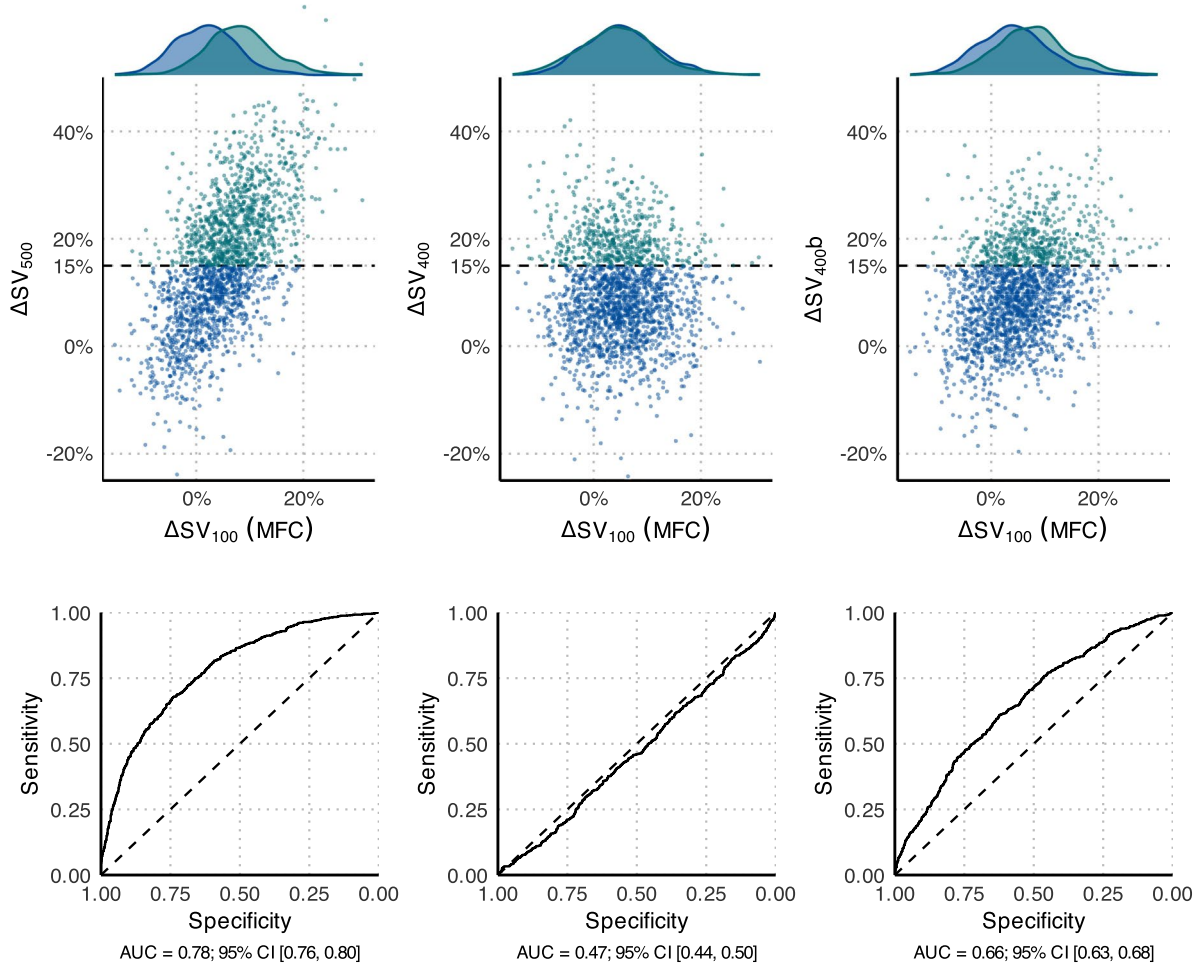

FIGURE 5 Results of simulation 2. Upper panels are scatter plots of the simulated data (n=2000) along with distributions of the responder and non-responder subpopulations. Lower panels are the corresponding ROC classification curves of ΔSV_{100} predicting fluid responsiveness (ΔSV_{500}, ΔSV_{400} and $\Delta SV_{400}b > 15\%$). The simulation identifies the same problem highlighted in Figure 3, although at a lower magnitude, indicating that the assumptions for the statistical modelling may be too conservative in comparison with the behaviour of real-world data

theoretically gives rise to a further overestimation of the classification accuracy in studies using the problematic MFC design, compared to the demonstrated overestimation in our simulation. The difference between predicting $\Delta SV_{500} > 15\%$ and $\Delta SV_{400} > 15\%$ is larger in the study by Muller et al than that in our simulations (see Figures 3–5). This can be explained by the combination of the shared error problem and the relatively large MFC response in the study by Muller et al. It is important to note that while ΔSV_{400} is a more *clinically* meaningful outcome to predict, we discourage using ΔSV_{400} as the outcome given the *mathematical coupling* still present due to the *shared constituent value* (SV_{100}). Neither of the two ROC curves in Figure 3 reveal the 'truth'.

4.2 | Designs with different monitoring modalities for predictor and outcome variables

In one study, authors used different monitoring modalities for predictor and outcome variables: changes in pulse pressure variation (ΔPPV) predicting fluid responsiveness (defined as change in cardiac output).[8] This approach has the advantage that baseline measurements of PPV and thermodilution-derived cardiac output (CO_{TD}) have separate measurement errors:

$$\text{Predictor: } \Delta PPV = PPV_{100} - PPV_{\text{baseline}},$$

$$\text{Outcome: } \Delta CO_{TD} = CO_{TD,500} - CO_{TD,\text{baseline}}.$$

This reduces the concern about spurious correlation/mathematical coupling. However, while measurement errors are no longer shared, fluctuating physiology over time may still couple different haemodynamic modalities measured simultaneously. Also, this design still includes the response to the MFC in the outcome. Unlike other fluid responsiveness approaches such as the passive leg raising (PLR) manoeuvre, the MFC induces an irreversible physiologic change (because 100 ml fluid is not subsequently removed from the bloodstream).