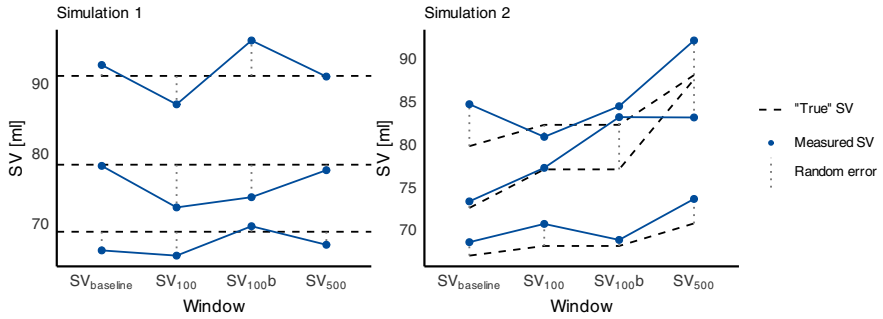

FIGURE 2 Illustration of how stroke volume (SV) measurements were simulated. Each panel shows three of 2000 simulated subjects. The dotted lines indicate the added random error at each time point

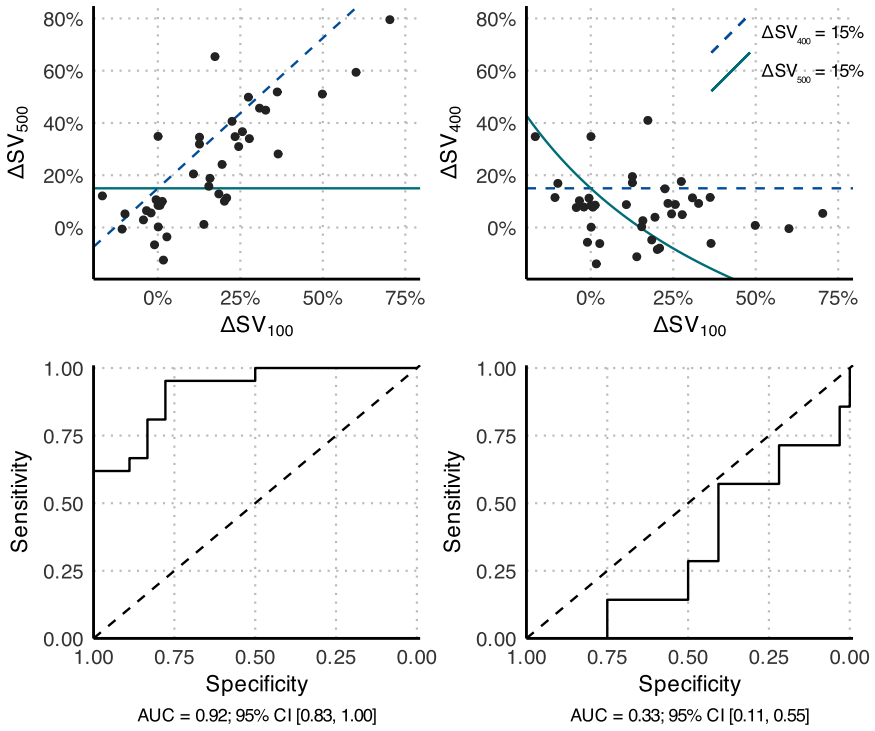

FIGURE 3 Reconstruction of data from figure 3A from Muller et al. (2011).[1] Upper panels: Scatter plots of the relation between ΔSV_{500} and ΔSV_{100} (left) and the relation between ΔSV_{400} (derived) and ΔSV_{100} (right). The full line represents the level at which ΔSV500 is 15% and the dashed line represents the level at which ΔSV_{400} is 15%. Lower panels: Corresponding ROC classification curves of ΔSV_{100} predicting $\Delta SV_{500} > 15\%$ and $\Delta SV_{400} > 15\%$ respectively

be impossible to predict which patients will have an increase in SV after 500 ml.

2.4.2 | Simulation 2

In a second, more realistic, simulation we simulated a 'true' response, still with additional random variation. Each subject was assigned an individual fluid response, which is the 'true' relative change from $SV_{baseline}$ to SV_{500} (the 'true' ΔSV_{500}). The simulated fluid response was drawn from a normal distribution (mean change = 15%, SD = 10%). To keep the simulation simple, the 'true' ΔSV_{100} was defined as 30% of this 'true' ΔSV_{500}:

'True' $SV_{baseline}$ was drawn from a normal distribution (mean = 75 ml, SD = 10 ml).

$$\text{'True' } SV_{500} = \text{'true' } SV_{baseline} \cdot (1 + \text{individual fluid response}).$$

$$\text{'True' } SV_{100} = \text{'true' } SV_{baseline} \cdot (1 + 0.3\ \text{individual fluid response}).$$

Independent random variation was subsequently added to each of these three 'true' measurements (mean = 0, SD = 3 ml) (see Figure 2). Again, we also simulated a second independent SV_{100} measurement (SV_{100}b) to serve as the reference measurement for an independent outcome measure (ΔSV_{400}b). An increase in SV of >15% was considered a significant positive fluid response in this *clinical* simulation.

3 | RESULTS

3.1 | Secondary analysis of an existing study

In Figure 3, plots are shown for ΔSV_{100}'s ability to predict $\Delta SV_{500} > 15\%$ (left panels) and ΔSV_{100}'s ability to predict $\Delta SV_{400} > 15\%$ (right panels). It is evident from Figure 3 that the classification goes from excellent (AUROC: 0.92) to worse than random (AUROC: 0.33) if SV_{100} is used as the reference value for the subsequent fluid response (ΔSV_{400}).