IDENTIFYING LACK OF ADHERENCE TO ANTIPSYCHOTIC TREATMENT USING PLASMA CONCENTRATION MEASUREMENTS

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Objective

To evaluate if measuring antipsychotic plasma concentrations using a diagnostic test can be used as a predictor of treatment adherence, and to identify the best plasma concentration threshold to reliably discriminate between adherence and partially non-adherent patients with schizophrenia.

Methods

▶ A population pharmacokinetic (PK) model for risperidone was used to simulate trough plasma concentrations (C_{trough}) of risperidone active moiety (risperidone + active metabolite 9-hydroxy-risperidone) for an oral dose of 4 mg under two different scenarios.
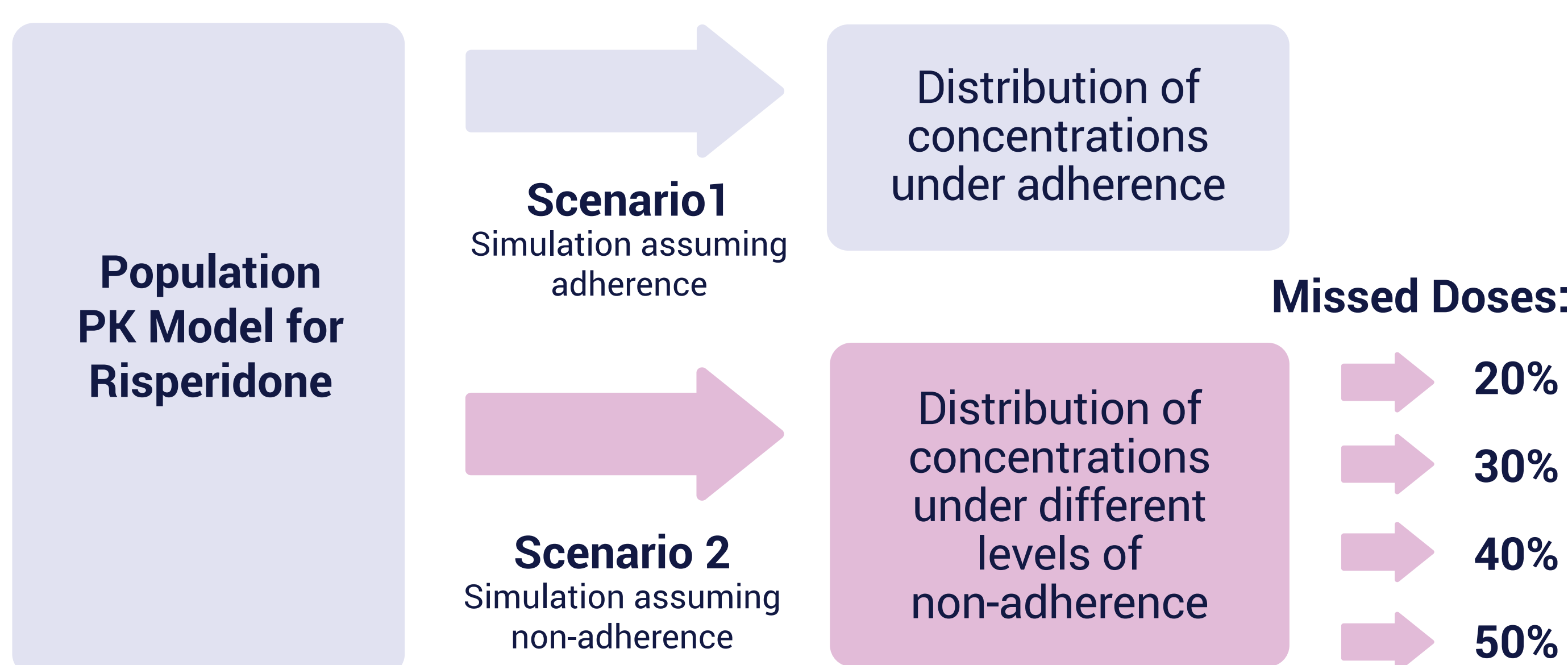

Figure 1   Schematic of the different simulated scenarios

▶ The first scenario assumed that all subjects had been adherent to their medication all of the time, whereas the second scenario assumed that 40% of the subjects had been non-adherent to their treatment, and randomly missed 20% to 50% of their doses over time at steady-state. [1]

▶ Based on C_{trough}, measured 24 hours after the last dose, the probability of being an adherent patient was calculated using a multivariate logistic regression model and assessed as a predictor of drug-treatment adherence by performing a receiver operating characteristic (ROC) analysis among the simulated patients under the two scenarios. [2,3]

▶ The area under the ROC curve (AUC_{ROC}), sensitivity, specificity, positive and negative predictive values were calculated and an assessment of the utility of multiple (vs single) drug concentrations of the diagnostic test was conducted. [4]

Results

TABLE 1   Diagnostic test parameters for a single drug concentration measurement used as predictor of drug-treatment adherence.

Diagnostic Test Parameters	Estimate	95% Confidence Interval (95%CI)
AUC_{ROC} %	71.2	68.6 - 72.4
Sensivity %	71.0	69.2 - 73.4
Specificity %	59.8	58.1 - 63.3
Positive predictive value, %	74.4	72.3 - 76.1
Negative predictive value, %	56.1	54.1 - 59.2

TABLE 2   Diagnostic test parameters for multiple (3) drug concentration measurements used as predictors of drug-treatment adherence. The 3 drug concentration measurements were used as an input of a multivariate logistic regression model and the probability of being an adherent patient was calculated.

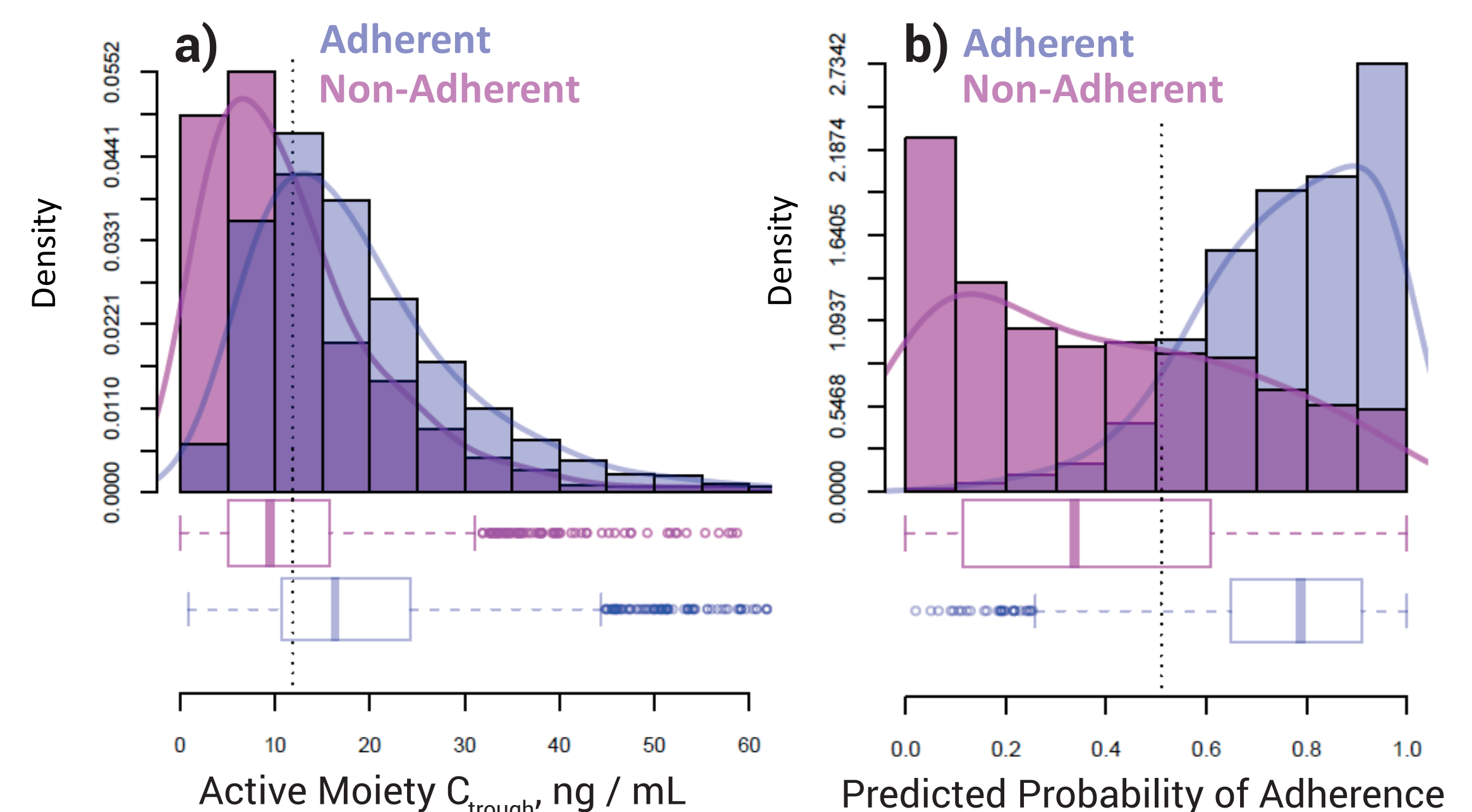| Diagnostic Test Parameters	Estimate	95% Confidence Interval (95%CI)
AUC_{ROC} %	85.2	83.9 - 87.3
Sensivity %	92.3	90.1 - 93.4
Specificity %	66.1	63.2 - 68.3
Positive predictive value, %	81.0	79.1 - 83.3
Negative predictive value, %	83.4	80.8 - 85.0

Results

Figure 2   Histograms and boxplots representing the distribution of the active moiety C_{trough} (a) and the model predicted probability of adherence (b) for adherent and non-adherent patients. The dashed vertical line represents the most efficient cut-off value where the lowest no. of misclassifications is achieved.
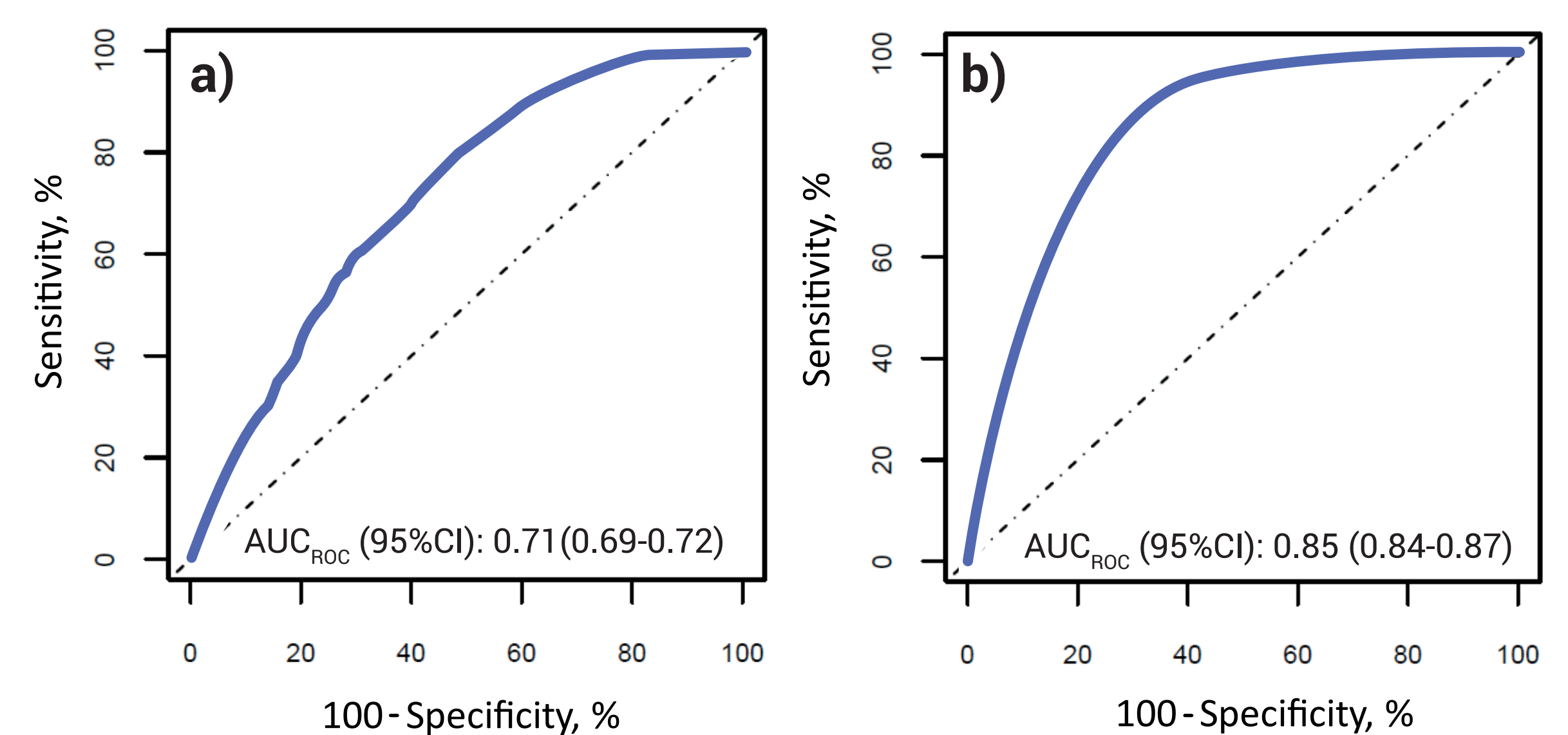

Figure 3   ROC curves representing the trade-off between sensitivity and specificity when a single (a) or multiple (b) drug concentration measurements are used as predictors of drug treatment adherence. The AUC_{ROC} shows that the level of accuracy of the diagnostic test increases when using multiple (vs single) drug concentrations.
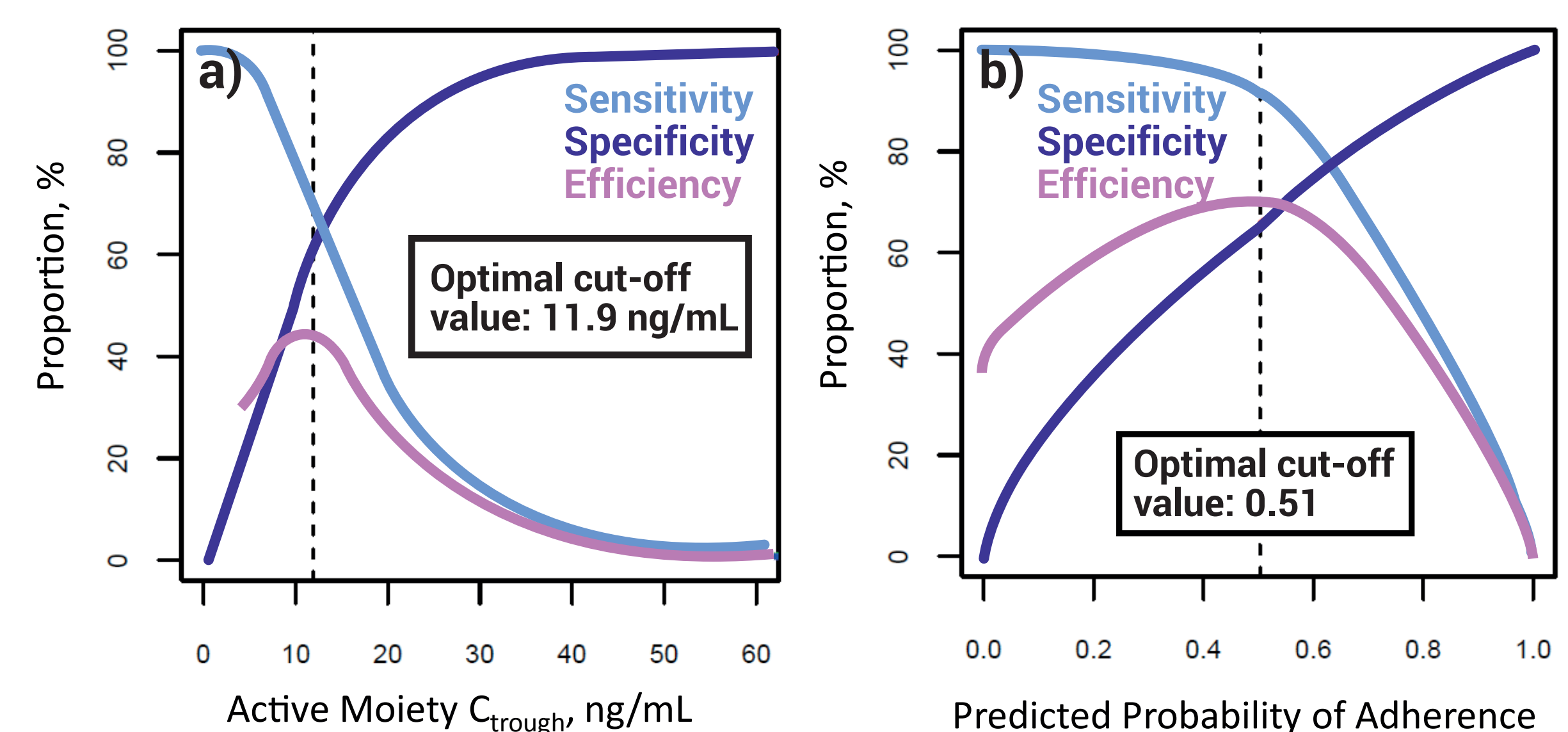

Figure 4   The sensitivity, specificity and efficiency were determined for each C_{trough} (a) and predicted probability of adherence (b) threshold. The dashed vertical line represents the most efficient cut-off value where the lowest level of misclassification is achieved.

Conclusions

The inclusion of 3 drug concentration measurements provides an accurate and precise diagnostic test, which enables to properly discriminate between adherent and non-adherent patients, if the non-adherent patients are missing at least 20% of the dose intakes.

References

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4. Greiner M, Pfeiffer D, Smith RD. Prev Vet Med. 2000; 45: 23-41.

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