Supplementary File, for online publication:

In this supplementary file, a further description is given of the bootstrapping technique and the generation of ROC curves from these bootstrapped data, including the calculation of grey zones.
In the peer-review process of this paper, one of the reviewers' comments was to provide a more detailed explanation of the bootstrapping technique, especially because figure 2 (which shows the *mean* ROC curves) can give the impression of confidence intervals that are provided with a coverage that is too narrow.
In order to reduce the length of the paper, we chose to provide only a brief description of the bootstrapping technique. Furthermore, we aimed to use exactly the same statistical methods as applied in a previous clinical paper in which the technique of providing grey zones from bootstrapped data, was applied (Ref #12, Cannesson et al, Anesthesiology 2011;115: 231-241). This way, we intended to provide results that permit a clear comparison with this paper, as well as we aimed to use "consequent" statistical methods in the literature.

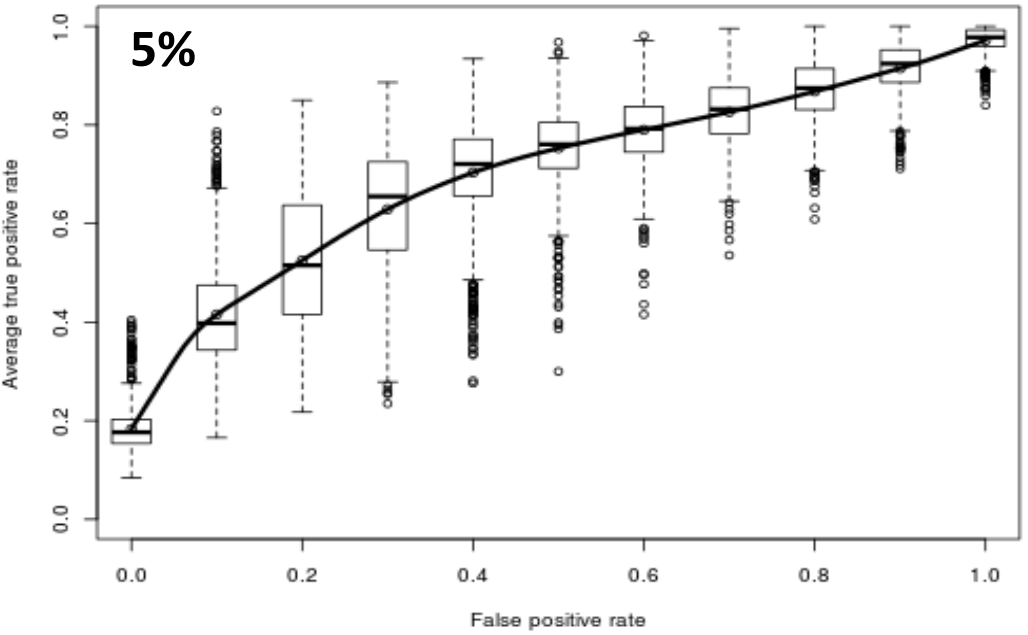
The bootstrapping technique is a *resampling* technique. From the observed data sample (here: the originally observed PPV and SVV values), a large number of resamples (of equal size to the original data sample, here: n=81) with replacement can be drawn. As these resamples are randomly drawn from the original data sample, the data distribution of these resamples will differ slightly from the originally observed data distribution, as per resample, some data points might be selected more than once, and other data points might not be selected. Therefore, the resulting bootstrapped data can be seen as a "model" for the true population data distribution. Therefore, the bootstrapping techniques limits the influence of outliers and can give a more "robust" impression of mean and variability.

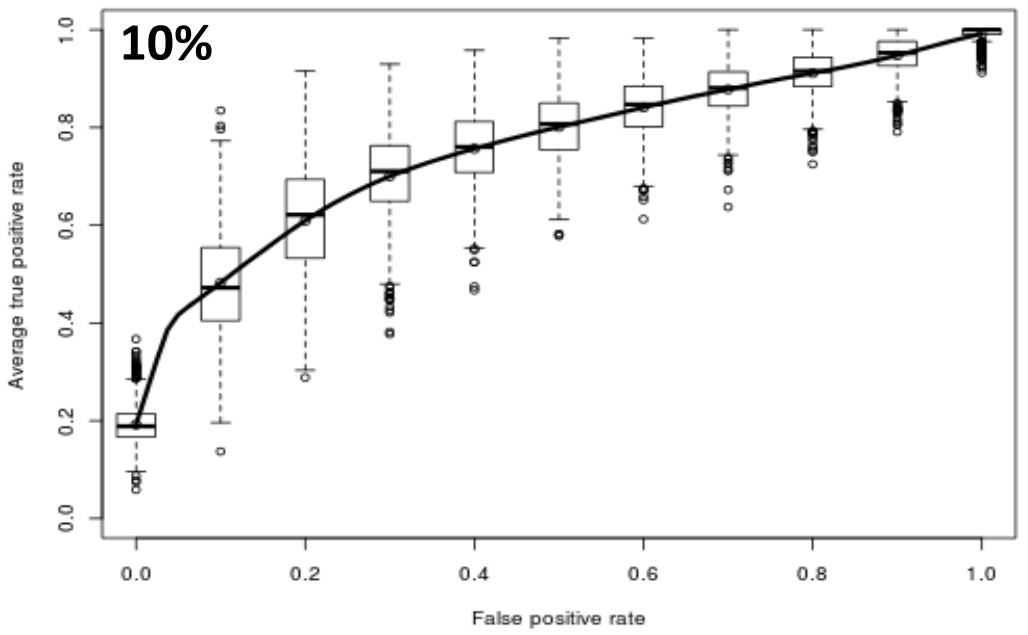
In this study, bootstrapping was performed by creating 1000 ROC curves, each of which consists of 81 data points with associated sensitivity and specificity values. This way, per SVI threshold (10,15,20 and 25%) and corresponding variable (PPV, SVV) response, 81000 combinations of sensitivity, specificity and test value were obtained.
Importantly, the ROC curves in figure 2 only provide the *mean* ROC curve per threshold, and therefore these ROC curves are very "smooth", which might appear unrealistic. In order to elucidate this more clearly, this supplementary file includes the original bootstrapped ROC curve plots, in which the bootstrap-derived data distribution of the ROC curves is clearly depicted; please see supplementary Figure 1A-B (SVV) and Figure 2A-B (PPV) for these ROC curves. The curves, generated for the 10-25 ↑SVI thresholds, depict the data distribution (represented by the boxplots) of the bootstrapped sensitivity / specificity data pairs. The ROC curves as depicted in figure 2 of the paper, represent the *mean* ROC curves from these original ROC curves. We however believe that implementing these original ROC curves in the paper itself would trouble a clear data presentation and therefore we have depicted the mean ROC curves in the paper. Therefore, we have added the original ROC curves for the

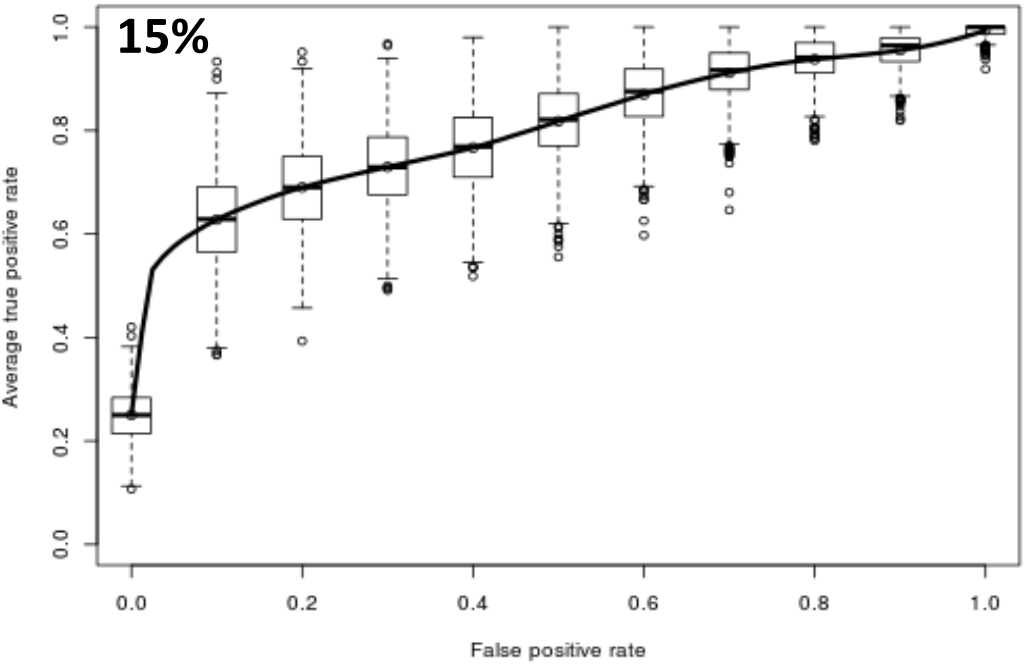
interested reader, in order to better understand the methods behind the generation of ROC curves from bootstrapped data.

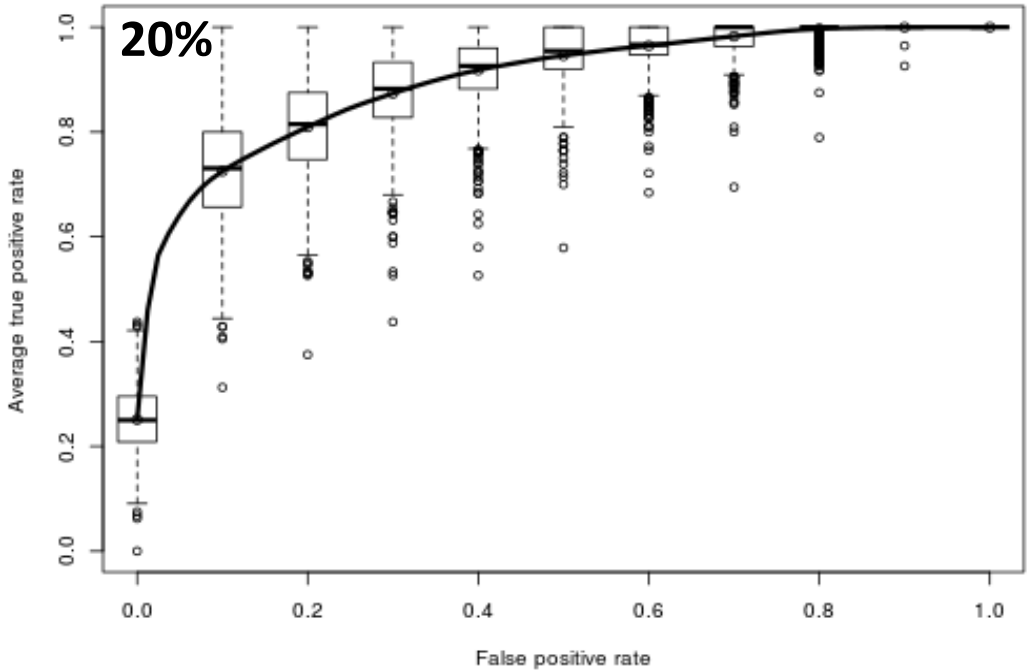
In accordance with the paper from Cannesson et al, we applied two methods for calculating the grey zone limits. The first method does not use confidence intervals but aims to detect test values for which either sensitivity or specificity is insufficient, i.e. is < 90% (of note: these were the sensitivity / specificity values derived after bootstrapping, see above). The second method uses confidence intervals, and it is calculated as the 95% confidence interval of the calculated optimal values. These optimal values were calculated from the Youden index values, which is calculated as sensitivity + specificity -1. These Youden- indices were calculated per bootstrapped sample of each ROC curve. Per ↑SVI threshold, the widest of the two resulting grey zones was chosen as the grey zone.

Supplementary Figure 1A (SVV)

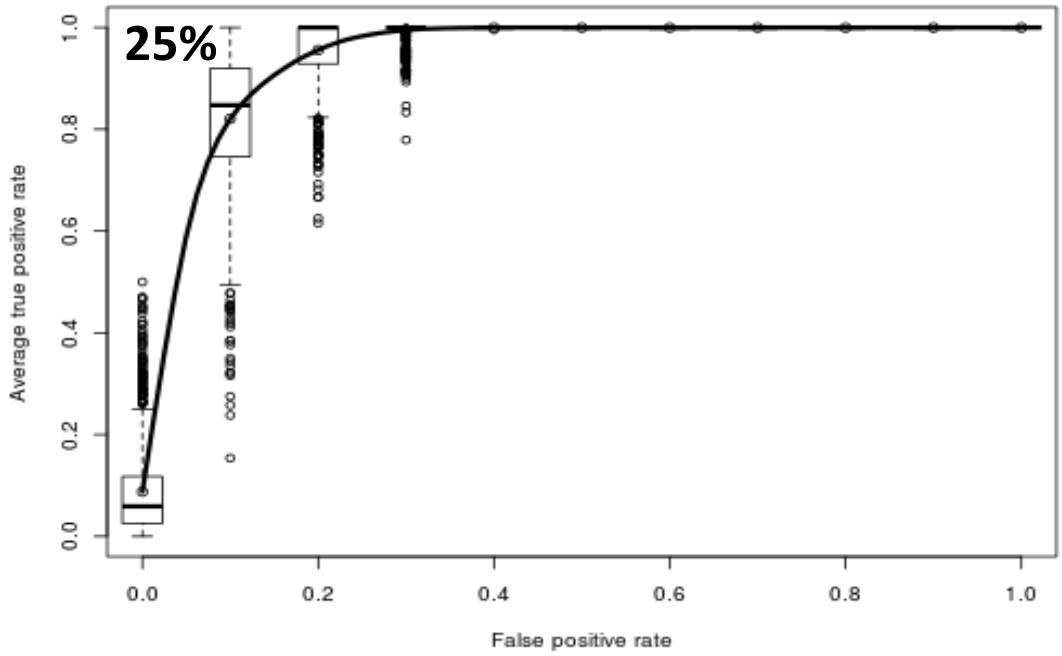




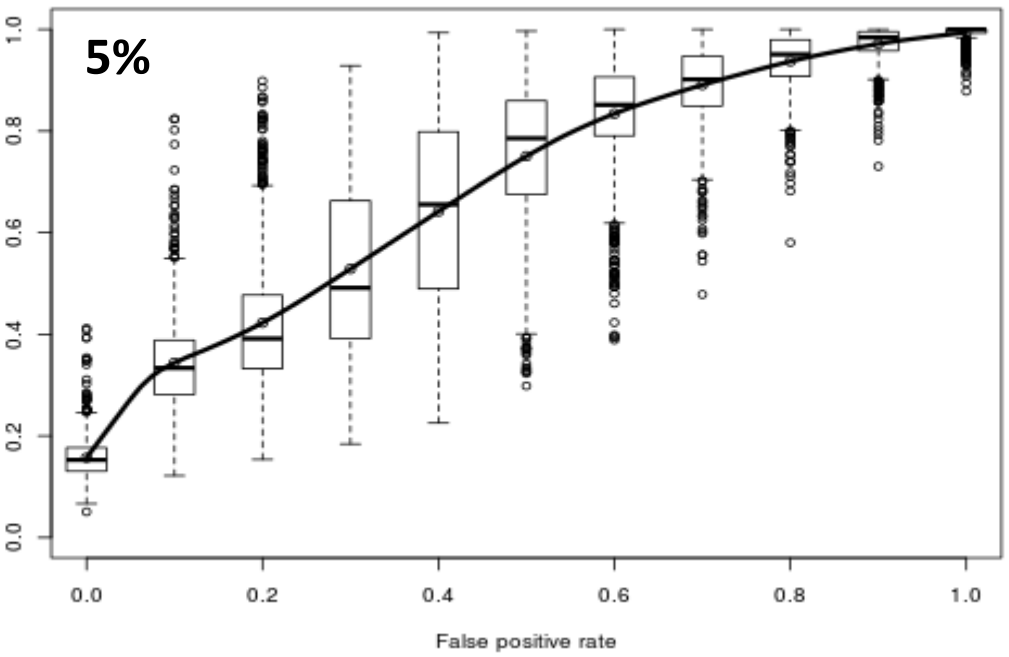


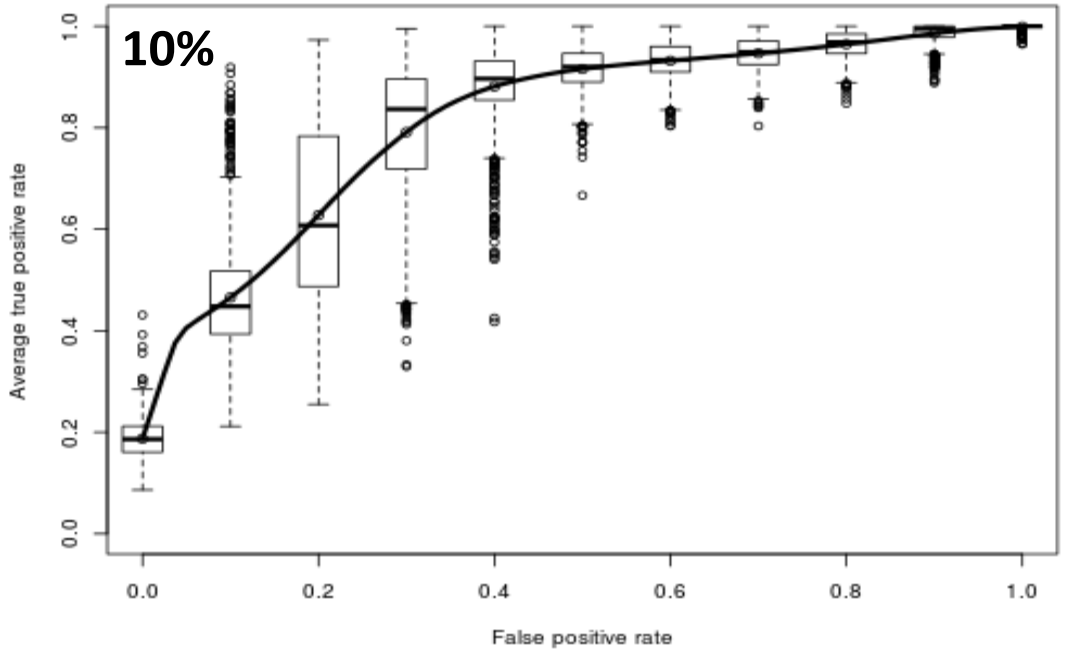


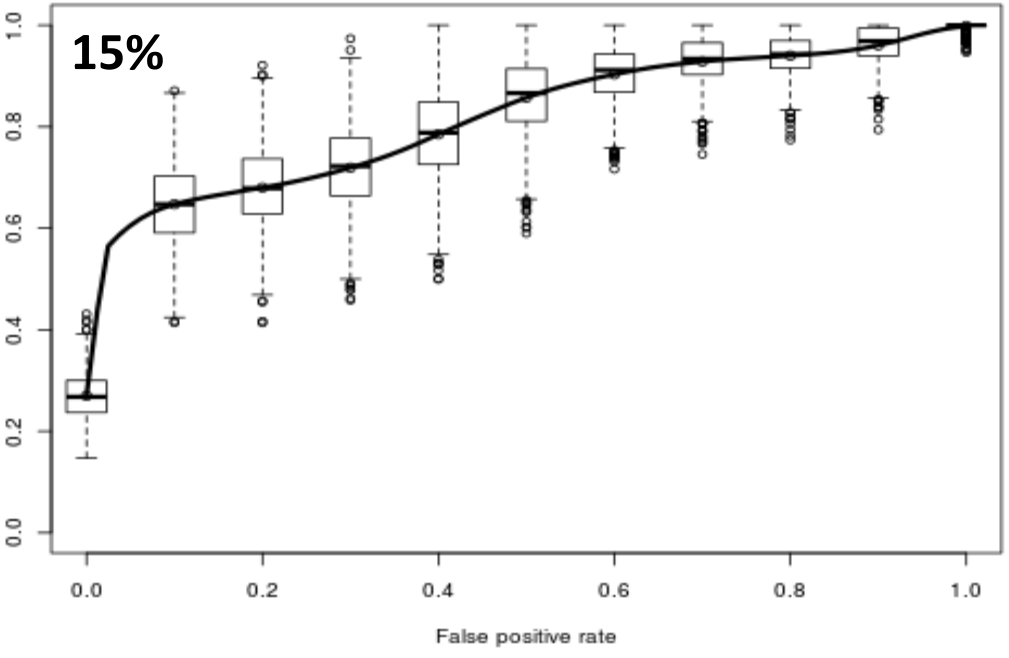
Supplementary Figure 1B (SVV)

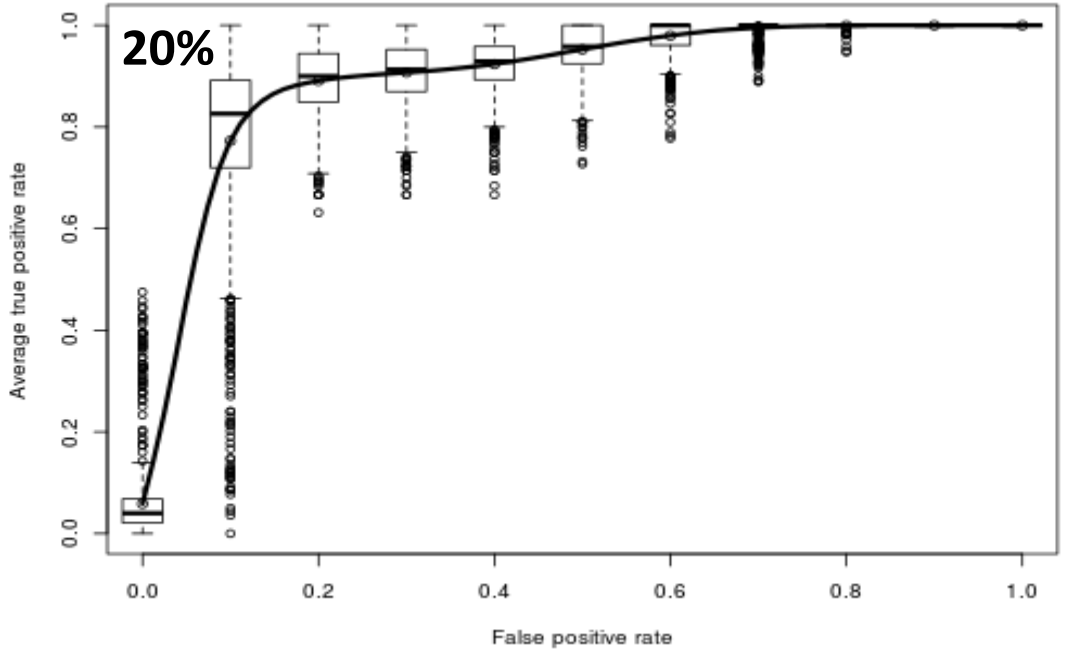


Supplementary Figure 2A (PPV)









Supplementary Figure 2B (PPV)