

# Performance of early cortisol measurements post transphenoidal surgery in predicting ACTH sufficiency in dynamic testing

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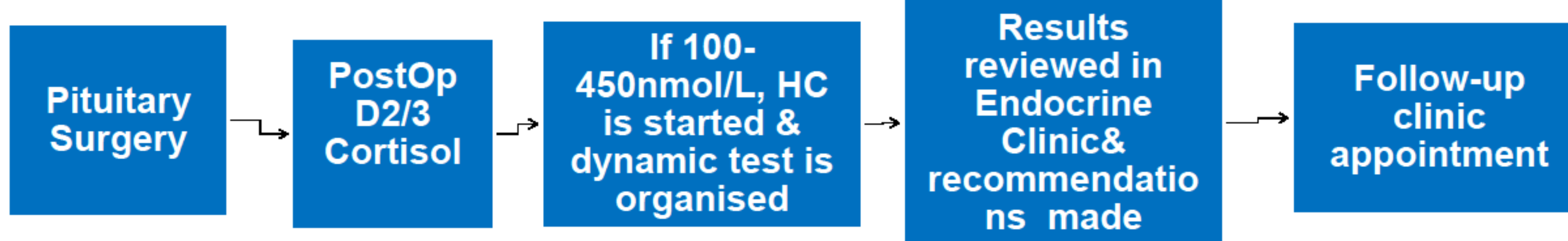
Topic: Pituitary Clinical

## Background

After pituitary surgery patients require HPA axis assessment, that is achieved with postoperative cortisol measurements and, in selected patients in whom post-operative cortisol measurements are inconclusive, with the insulin tolerance test (ITT) and the glucagon stimulation test (GST).

In order to identify patients with ACTH deficiency following pituitary surgery in our centre, a day 2 or 3 (D2/3) 8-9am cortisol is measured: if D2/3 cortisol is  $<100\text{nmol/L}$ , HC replacement is commenced, and if D2/3 cortisol is  $>450\text{nmol/L}$  patients are classified as ACTH sufficient. In patients with a D2/3 cortisol  $100\text{-}450\text{nmol/L}$ , dynamic testing with an ITT or GST is used, in order to identify patients with ACTH deficiency who require glucocorticoid replacement. In patients with epilepsy, ischaemic heart disease, or above the age of 65, the GST is used instead of the ITT. We use a peak cortisol of  $\geq 550\text{nmol/L}$  for both tests to indicate ACTH sufficiency.

## Figure 1. Protocol for testing for hypocortisolism following Pituitary Surgery



## Aim

To assess the performance of the D2/3 post-operative cortisol in predicting the HPA axis sufficiency as assessed by the ITT and the GST.

## Methods

Retrospective review of all dynamic testing results post pituitary surgery between 2004-2014 in a tertiary centre, and of the medical notes. Data captured included comorbidities, medications, cortisol results in the immediate post-operative period, and length of follow-up.

Patients with Cushing's disease, incomplete data, or those who did not reach adequate hypoglycaemia on ITT were excluded. Data were analysed with Excel and XLSTAT, and are presented as mean  $\pm$  SD. Fitted receiver operator characteristic analysis was done with the calculator available on <http://www.jrocfit.org>, graphs were prepared in Excel and depict the true positives (TP) with 95% upper and lower confidence intervals (CIs).

## Results

- 71 patients met the inclusion criteria, out of which 41 (57.7%) had an ITT and 30 (42.3%) a GST.
- 9am cortisol measurements on day 2/3 postoperatively did not differ between the patients having an ITT or a GST ( $353\pm 188\text{nmol/L}$  vs  $348\pm 194\text{nmol/L}$ ,  $p=0.85$ ).
- 25 patients passed the ITT and 12 passed the GST, using a cortisol cut-off of  $\geq 550\text{nmol/L}$ .
- Peak cortisol measurements post dynamic testing were  $549\pm 218\text{nmol/L}$  for ITT and  $458\pm 241\text{nmol/L}$  for GST.
- Using a cut-off in dynamic testing of  $>550\text{nmol/L}$  for ACTH sufficiency, ROC curve analysis showed that day 2/3 postoperative cortisol of  $\leq 142\text{nmol/L}$  was 100% (84-100%) sensitive in detecting patients that would fail the ITT, with 31% (14-56%) specificity, and a cut-off of  $\geq 470\text{nmol/L}$  was 94% (69-100%) specific in identifying patients with ACTH sufficiency with 32% (17-52%) sensitivity (Figure 2).
- When applying the same cut-offs in GST, a day 2/3 cortisol of  $\leq 142\text{nmol/L}$  was 93% (62-100%) sensitive in detecting patients that would fail the GST, with 28% (12-51%) specificity, and a cut-off of  $\geq 470\text{nmol/L}$  was only 78% (54-91%) specific in identifying patients with ACTH sufficiency with 50% (26-75%) sensitivity.
- In some centres a lower cortisol cut-off in dynamic testing is used. We therefore retrospectively applied a cortisol cut-off of  $>500\text{nmol/L}$  for a positive ITT or GST, in order to examine if the performance of the D2/3 cortisol in predicting the outcome of dynamic testing improves (Figure 3). This increased the area under the curve for the GST, but did not improve further area under the curve for the ITT.

## References

- Eng J. ROC analysis: web-based calculator for ROC curves. Baltimore: Johns Hopkins University [updated 2014 March 19; cited 2015 May 04]. Available from: <http://www.jrocfit.org>.
- Arti W, Allolio B. Adrenal Insufficiency. Lancet 2003;361:1881-93.
- Jayasena CN et al. Day 5 Morning Serum Cortisol Predicts Hypothalamic-Pituitary-Adrenal Function after Transsphenoidal Surgery for Pituitary Tumors. Clinical Chemistry 2009;55:5:972-977.

## ROC Curve for D2/3 Cortisol in the ITT group (550nmol/L)

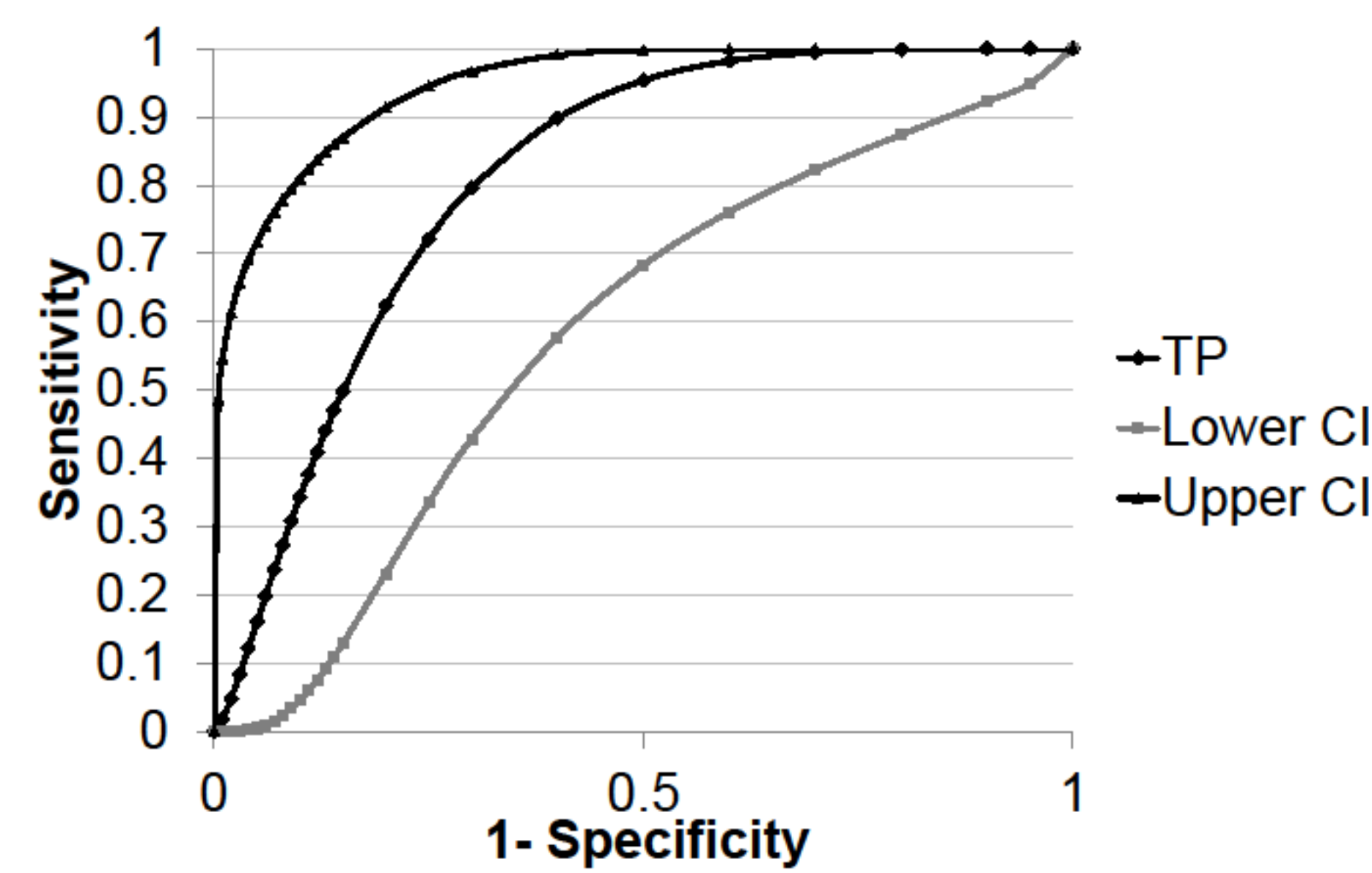
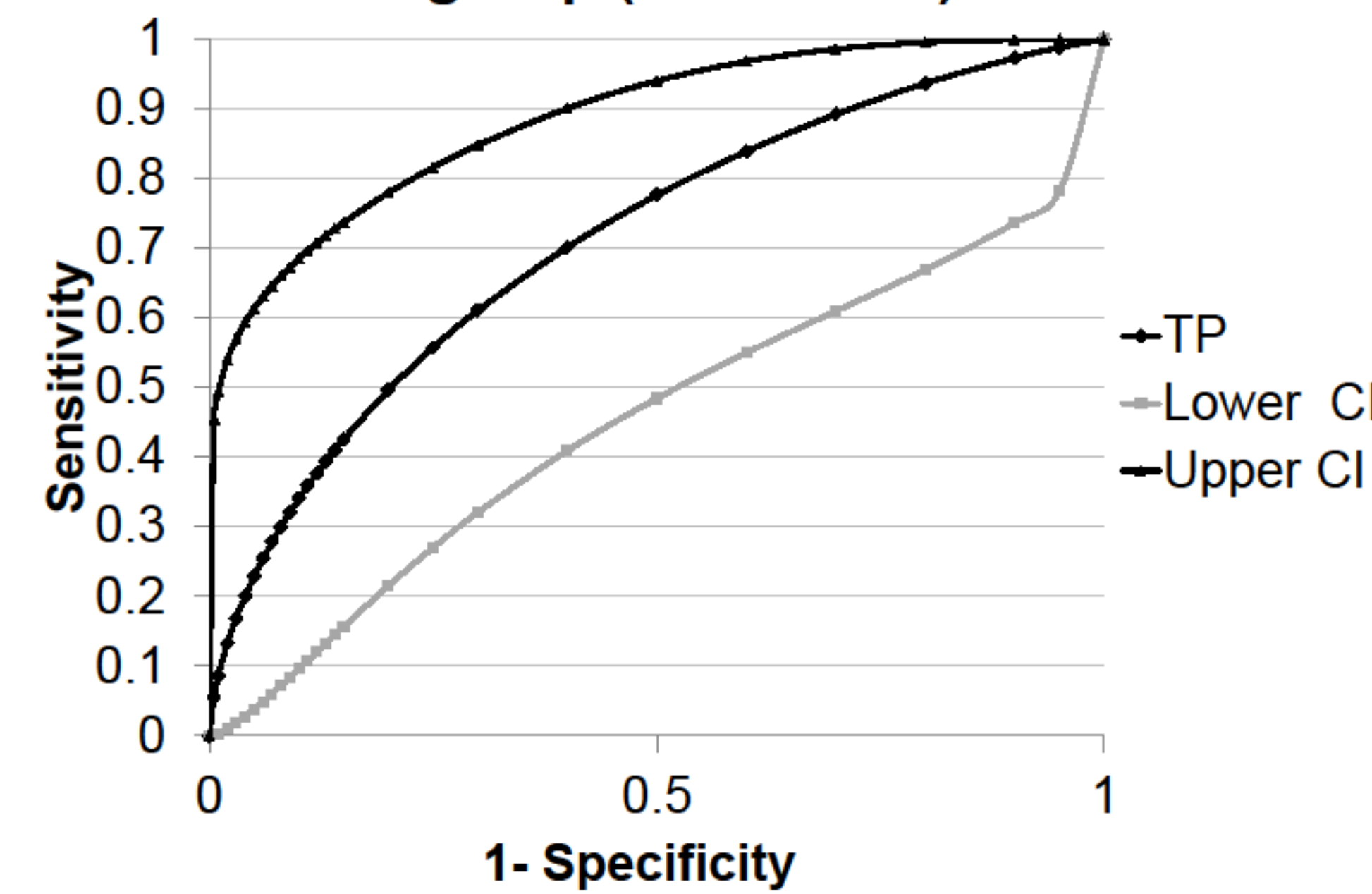


Figure 2. ROC curve analysis using as cut-off a cortisol  $> 550\text{nmol/L}$

Area under the curve: 0.811

## ROC Curve for D2/3 Cortisol in the GST group (550nmol/L)



Area under the curve: 0.721

## ROC Curve analysis for D2/3 cortisol in the ITT group (500nmol/L)

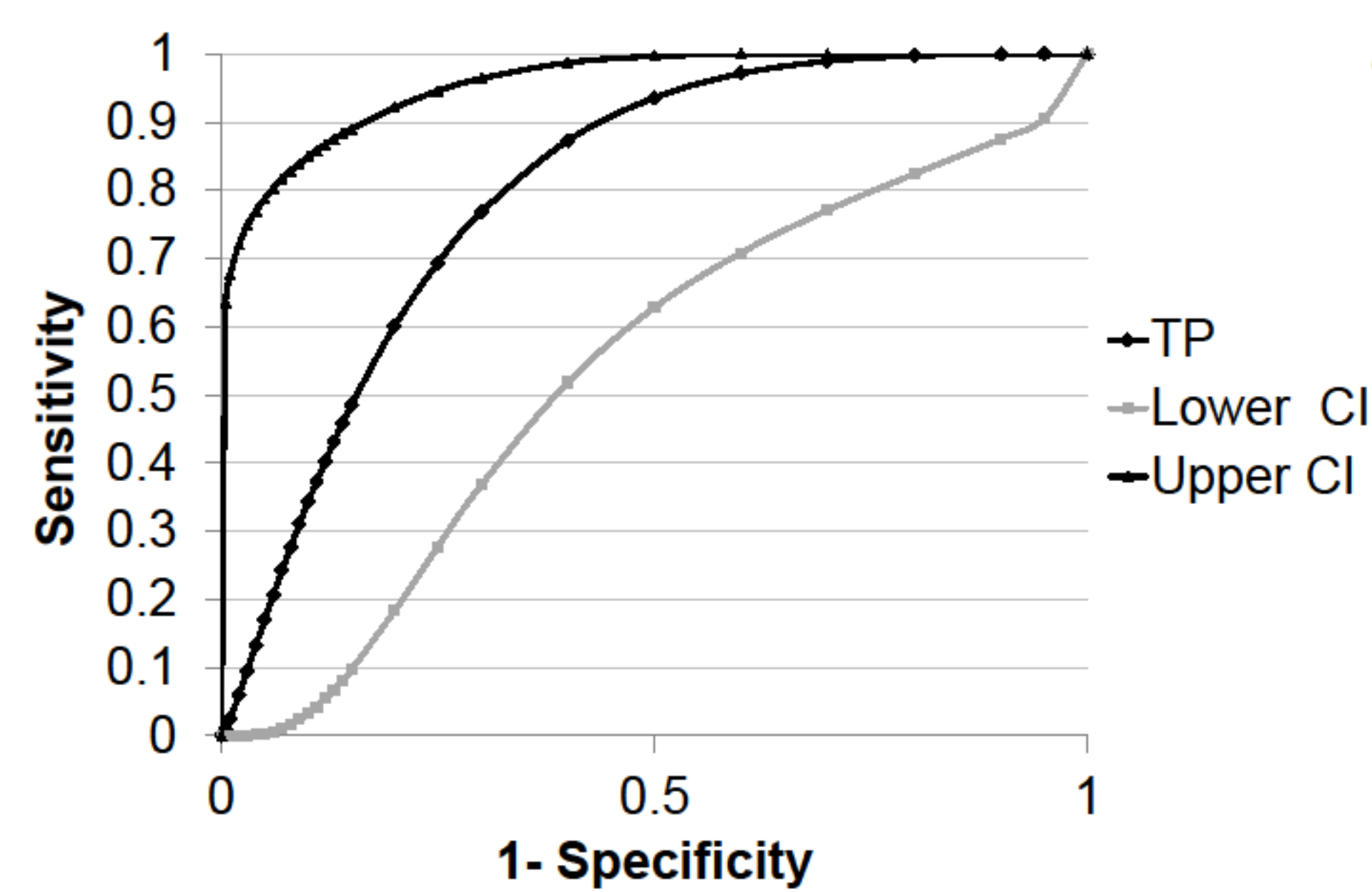
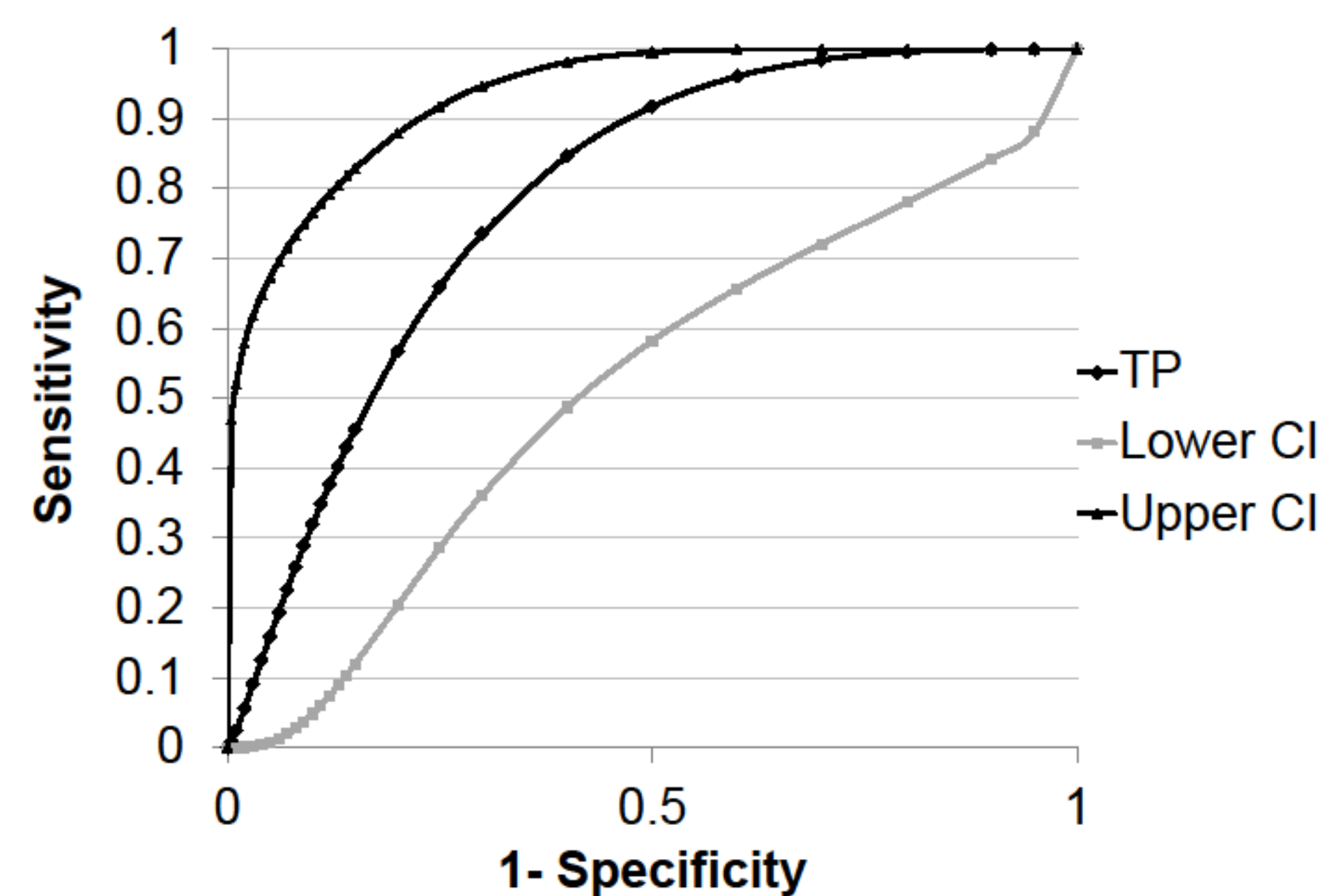


Figure 3. ROC curve analysis using as cut-off a cortisol  $> 500\text{nmol/L}$

Area under the curve: 0.8001

## ROC Curve analysis for D2/3 cortisol in the GST group (500nmol/L)



Area under the curve: 0.785

## Conclusions

After pituitary surgery a D2/3 postoperative cortisol of  $\leq 142\text{nmol/L}$  detects all patients with ACTH insufficiency, and a cortisol of  $\geq 470\text{nmol/L}$  excludes ACTH deficiency.

Changing the cortisol cut-off for dynamic testing from 500 to 500nmol/L, improves the performance of the D2/3 cortisol in predicting the GST result, but not the ITT result.

Compared to previous studies that examined the performance of D5 postoperative cortisol in predicting the result of dynamic testing, the higher D2/3 cortisol found to predict ACTH sufficiency here, may be due to higher cortisol measurements occurring early after surgery.

