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ORIGINAL ARTICLE

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Redefining ITT cortisol thresholds on Abbott platforms to prevent misdiagnosis of adrenal insufficiency

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Abstract

Background: Adrenal insufficiency (AI) is a life-threatening condition which requires long term glucocorticoid replacement. The insulin tolerance test (ITT) is the current gold standard test for diagnosis of secondary AI, but the widely accepted cut-off value of a peak cortisol of less than 500 nmol/L assumes that anyone who does not reach this value has AI and thus requires full replacement. The cut-off used to diagnose AI is also founded on outdated assays. Use of this cut-off in an era of more specific immunoassays therefore risks misdiagnosis, subsequent unnecessary glucocorticoid exposure and associated adverse effects with increased mortality risk.

Design, Patients and Measurements: This retrospective analysis assessed 300 ITT cortisol responses using the Abbott Architect and Alinity analyser platforms in patients with suspected AI over a period of 12 years (August 2010 to January 2022), at a tertiary centre.

Results: Patients were classified as having AI or not, based on a comprehensive clinical review of electronic patient records from the point of test to the present day by a panel of pituitary and adrenal specialists. Using the current institutional cut-off value of 500 nmol/L, receiver operating characteristic analysis identified a 100.0% sensitivity and 43.6% specificity (area under the curve 0.979). Using a lower cortisol threshold value of 416 nmol/L on the Abbott analyser platform maintained a sensitivity of 100.0% and improved the specificity to 86.7%.

Conclusion: This data supports lowering the Abbott analyser ITT peak cortisol threshold to 416 nmol/L. Use of this improved cut-off avoids unnecessary glucocorticoid replacement therapy in 104 (34.7%) of individuals in this study. All patients remained well with at least 1 year longitudinal follow up of glucocorticoid replacement.

KEYWORDS

adrenal insufficiency, adrenocorticotropic hormone, glucocorticoid replacement, insulin tolerance test

1 | INTRODUCTION

Adrenal Insufficiency (AI) is a potentially life-threatening disease caused by primary or secondary failure of the adrenocortical cells. Patients with primary AI are at risk of an Addisonian crisis if they do not have a full replacement dose of both cortisol and aldosterone. The treatment of secondary AI should be more nuanced, especially in those with partial AI where there is some adrenal reserve. Although the outcome of AI has vastly improved since the introduction of glucocorticoid replacement therapies, it has become evident that patients treated with glucocorticoids for AI are frequently exposed to glucocorticoid excess.[1] Replacement therapy is unable to fully replicate a normal endogenous circadian and ultradian rhythm.[2] Even mild glucocorticoid excess is associated with the development of cardiovascular disease, diabetes mellitus and risk of osteoporosis. These sequelae have a significant impact on patients' quality of life and provoke an increased all-risk mortality.[3–6] There is therefore a need to ensure that patients are not incorrectly labelled with an AI diagnosis, thereby exposing them to inappropriate glucocorticoid replacement therapy and the increased morbidity and mortality associated with this.

At present the gold standard test for assessment of the integrity of the hypothalamic-pituitary-adrenal (HPA) axis is an insulin tolerance test (ITT). This assesses the cortisol response to insulin-induced hypoglycaemia.[7] Patients who do not achieve an appropriate peak cortisol level during the test are labelled with AI and may then be placed on a full and thus suppressive replacement dose of glucocorticoid.

A peak cortisol value of >550 nmol/L was initially established by Plumpton and Besser, who in 1969 evaluated the cortisol responses to insulin induced hypoglycaemia and major surgery in normal and glucocorticoid-treated patients. They proposed a cut-off value of 550 nmol/L as the minimum cortisol value required for healthy individuals to reach during an ITT.[8]

This cut-off was set at a time when it was felt that replacement therapy had no risks, and that the risk of an Addisonian crisis was to be avoided at all costs by erring on the side of over-replacement. The cut-off was determined using less specific fluorometric assays producing a 20–30% positive bias compared with the current more specific immunoassays. Recognition of this fact has led to variability of cut-off recommendations which range from 500 to 550 nmol/L.[9] Use of these outdated cut-offs in an era of more specific immunoassays risks misdiagnosis and subsequent unnecessary glucocorticoid exposure. Updated assay-specific cut-offs should therefore be established to ensure accurate interpretation. Considering the development of newer more specific assays, use of this threshold risks inappropriately labelling healthy individuals with AI. There remains a need, however, to ensure patients with true AI are not missed.

Imperial College Healthcare NHS Trust (ICHNT) guidelines currently use a peak cut-off value of ≤500 nmol/L to make a diagnosis of AI, but also allow clinicians to use clinical judgement when the peak cortisol is anywhere between 375 and 500 nmol/L.[10]

We hypothesised that the specificity of the current cut-off of 500 nmol/L could be increased by using a lower cut-off value, without compromising sensitivity. We therefore aimed to assess the current sensitivity and specificity at the 500 nmol/L cut-off value to determine the most appropriate cut-off point to offer improved specificity whilst maintaining sensitivity.

2 | METHODS

2.1 | Design

This was a retrospective study of all ITTs performed at Imperial College Health care NHS Trust. Data was collected from August 3, 2010 to January 27, 2022. Before this, the Siemens Immulite 2000 and Olympus platforms were used at different sites. This was harmonised to the Abbott Architect platform between 2009 and 2010. Patient cortisol and glucose results were extracted from baseline, 30-, 60-, 90-, 120-min values. Patients' age, indication for performing the ITT and length of follow up were recorded.

Patients were excluded if there was a failure to achieve adequate hypoglycaemia (<2.2 mmol/L) together with an inadequate cortisol rise (≤500 nmol/L), or if the ITTs were conducted outside of ICHNT and if there were no updated patient records. Patients were also excluded if they were on oral oestrogen therapy, combined oral contraceptive, or had a diagnosis of active Cushing's Disease.

For the assessment of baseline cortisol as a predictor of ITT results, only morning ITTs were included. Where times were not specified, the assumption was made that these took place in the morning as per our local ITT protocol.

A diagnosis of AI was made by clinical review, which was based on a comprehensive review of patient electronic records by the authors A. H. and K. L. Where misdiagnosis was suspected, the patient notes were reviewed by a panel of endocrinologists to evaluate all patient records, including longitudinal clinical data to date of review. Where patients underwent additional biochemical tests, these were arranged by the treating clinician at the time. All patients were followed up for a minimum of 1 year. The term clinical review is used to refer to this throughout the rest of the paper. This study was completed as a registered service evaluation within ICHNT (ref: END_014).

2.2 | Assay methodology

Serum total cortisol was measured on Abbott Architect or Abbott Alinity analyser platform immunoassays. These have intra- and inter-assay coefficients of <5.5% and <6.2%, and <4.3% and <5.1% respectively. Both assays have a lower limit of quantification of 28 nmol/L. A phased transition from Abbott Architect to the Abbott Alinity platform occurred between 2018 and 2019 across all Imperial College Healthcare Trust Sites. Validation against the previous Architect analysers was completed in compliance with ISO15189. As the results generated on the Alinity analysers are directly comparable to the previous Architect analysers, there has not been a change in the local reference ranges or cortisol cut-off values.

2.3 | Statistical analysis

Patients were initially categorised into four groups based on peak cortisol levels reached during the ITT and the subsequent diagnosis made, based on comprehensive clinical review. These comprised: (1) true positive (cortisol ≤ 500 nmol/L and with clinical diagnosis of AI), (2) false positive (cortisol ≤ 500 nmol/L without clinical diagnosis or evidence of AI), (3) true negative (cortisol > 500 nmol/L without clinical diagnosis or evidence of AI), and (4) false negative (cortisol >500 nmol/L with clinical diagnosis or evidence of AI). Data was filtered using Microsoft Excel 365 and statistical analyses performed using GraphPad Prism version 9.3.1 (GraphPad).

Area under the curve (AUC) was calculated for the receiver operating characteristic (ROC) generated and used as a summary measure of performance using Prism 9. Normality was assessed

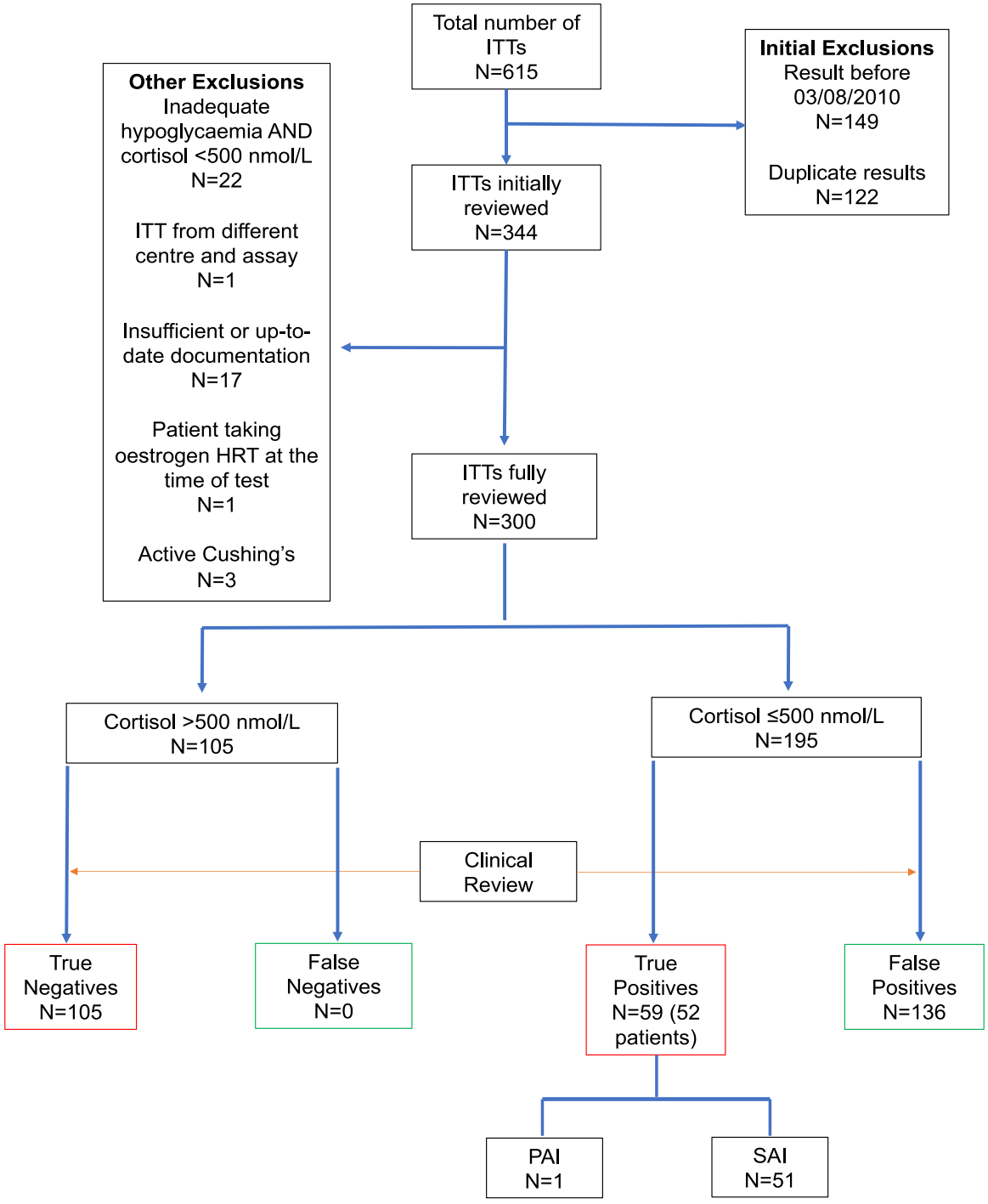

FIGURE 1 STROBE Diagram outlining the study design. Note that of the 59 true positive ITTs, these were performed in 52 patients in total. HRT, hormone replacement therapy; ITT, insulin tolerance test; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

using the Shapiro–Wilk test. Variables are presented as mean (±standard deviation) where normally distributed. Nonparametric data sets are presented as median (interquartile range). Statistical significance was reported at an alpha level of 5%.

3 | RESULTS

A total of 615 ITTs were initially reviewed, of which 300 ITT results from 260 individuals were reviewed and included within the study analysis.

There were 149 ITTs performed before August 2010 when the assay changed to the Abbott platform and were therefore excluded. A total of 122 results were duplicated and excluded. Another 22 ITTs failed to reach a nadir glucose ≤ 2.2 mmol/L with a cortisol rise ≤ 500 nmol/L and were also excluded. There was one ITT that was conducted outside of ICHNT and 17 ITT results for patients without updated electronic medical records. Additionally, one ITT was completed whilst the patient was on oestrogen replacement and another three patients had active Cushing's Disease at the time of the ITT (Figure 1).

Of the 260 individuals included within the analysis, there was a median (IQR) follow up-duration of 6.67 (4.67) years and a mean (±standard deviation) age of 41.75 (±11.80) years.

3.1 | Diagnosis of AI

A peak cortisol value of ≤500 nmol/L was assessed, as it is the current cut-off point utilised for making an AI diagnosis on ITT. This was based on a comparative internal study of the performance of the Abbott Architect immunoassay versus the Siemens Immulite 2000 assay in 2010, which showed that an Abbott cortisol result of 500 was equivalent to 550 nmol/L in the Immulite assay.

A total of 59 ITTs (19.7%) were completed in 52 patients who were clinically classified as having AI, requiring glucocorticoid replacement therapy. These were classified as true positives. Of these true positive results: one patient was diagnosed with primary AI and 51 patients had a diagnosis of secondary AI (Table 1). Thirty-four patients with a diagnosis of secondary AI had undergone transsphenoidal surgery. Three patients with SAI had undergone previous radiotherapy.

A total of 195 ITT results (65%) had a peak cortisol ≤ 500 nmol/L, of which 136 results were from patients with no evidence of AI upon clinical review and were therefore classified as false positives. Ninety-one patients underwent additional biochemical testing (66.9%); this included 34 (28.8%) short Synacthen tests (SST), 21 (17.8%) overnight metyrapone suppression tests and 24 (20.3%) glucagon suppression tests.

All 105 patients (34.8%) who achieved a peak cortisol > 500 nmol/L showed no biochemical or clinical evidence of AI upon review and were considered as true negatives. No false negative cases were detected.

Using a cortisol cut-off value of 500 nmol/L therefore determined a 100.0% sensitivity and a specificity of 43.6% in correctly diagnosing AI.

TABLE 1 Breakdown of causes of adrenal insufficiency by type (52 patients with 59 true positive ITT results).

Classification of adrenal insufficiency	Causes
Primary	x1 autoimmune hypoadrenalism
Secondary	x3 panhypopituitarism (undetermined cause)
	x36 pituitary adenomas
	x1 Langerhans histiocytosis
	x3 traumatic brain injury
	x1 Rathke's cleft cyst
	x3 pituitary apoplexy
	x1 hypophysitis
	x1 isolated ACTH deficiency
	x1 empty sella
	x1 Sheehan's syndrome

Abbreviations: ACTH, adrenocorticotropin; ITT, insulin tolerance test.

This resulted in a negative predictive value (NPV) of 100.0% and a positive predictive value (PPV) of 30.3% (Table 2).

3.2 | ROC analysis of peak cortisol levels on ITT

The sensitivity and specificity of the ITT was calculated for each of the peak cortisol cut-off values and plotted on a ROC curve (Figure 2A). This produced an AUC of 0.979 ($p < .0001$).

ROC analysis showed that a peak cortisol value of ≤409 nmol/L demonstrated a sensitivity of 96.4% and a specificity of 88.6%. Although greater than the universally accepted ≥ 95% sensitivity, this value would still result in several false negative diagnoses (patients with AI being labelled as non-AI).

Increasing this to ≤416 nmol/L allows for a sensitivity of 100.0% and a specificity of 86.7%, therefore avoiding missed diagnoses of AI (Figure 2B). This results in an NPV of 100.0% and PPV of 64.8%. A peak cortisol value of >416 nmol/L using an Abbott immunoassay can therefore be used to exclude AI (Table 2).

3.3 | Baseline cortisol as a predictor of magnitude of cortisol rise

Figure 3 shows the cortisol profiles (median cortisol values with 95% confidence intervals) for all ITT results, according to a peak cortisol response using a cut-off cortisol value of 416 nmol/L.

Although there is an overlap for each group at 0- and 30-min, there is a subsequent rise with peak cortisol at 60 min at each group, with the higher baseline cortisol values showing a greater magnitude of rise. The magnitude of the rise in those

TABLE 2 Classification of patient cortisol values under the criteria for true positive, false positive, true negative and false negative using a cortisol cut-off of 500 and 416 nmol/L.

	Treated as AI	Not AI	*Total*
Cortisol ≤ 500 nmol/L	True Positive 59	False Positive 136	*Positive Tests 195*
Cortisol > 500 nmol/L	False Negative 0	True Negative 105	*Negative Tests 105*
Total	*With Disease 59*	*Without Disease 241*	Total Tests 300
Cortisol ≤ 416 nmol/L	True Positive 59	False Positive 32	*Positive Tests 91*
Cortisol > 416 nmol/L	False Negative 0	True Negative 209	*Negative Tests 209*
Total	*With Disease 59*	*Without Disease 241*	Total Tests 300

Note: A cut-off of 500 nmol/L results in a negative predictive value (NPV) of 100.0% and a positive predictive value (PPV) of 30.3%. Lowering the cut-off to 416 nmol/L improves the specificity to 86.7% and the PPV to 64.8%.

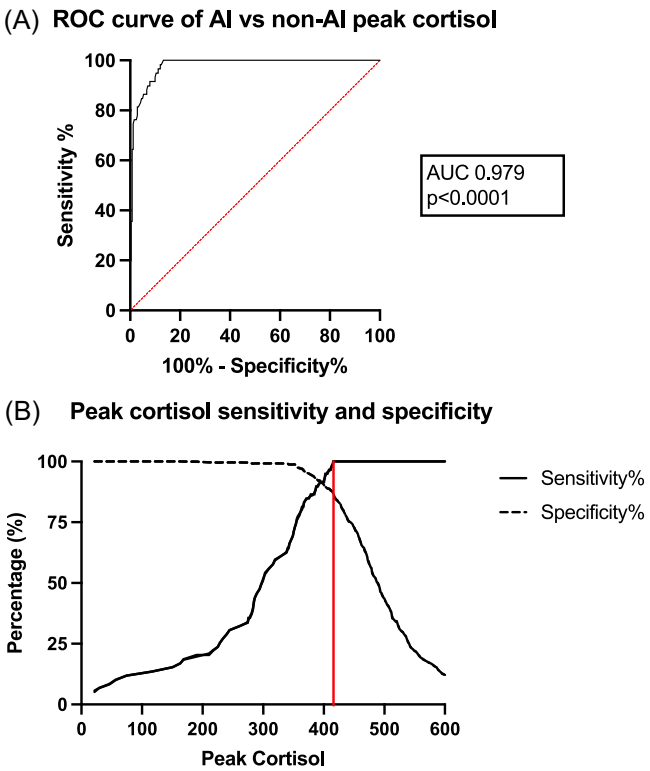

FIGURE 2 (A) Receiver-operator characteristic curve indicating the peak cortisol levels achieved on the insulin tolerance test for the diagnosis of adrenal insufficiency. Area under the curve (AUC) has been labelled on the graph. (B) Sensitivity and specificity profile of peak cortisol levels achieved on the insulin tolerance test. The point at which a sensitivity of 100% is achieved at the lowest peak cortisol level (416 nmol/L) is demarcated by the red line.

patients without AI (true negative and false positive results), however, is greater than those with a diagnosis of AI (true positive group).

3.4 | Use of baseline cortisol in predicting ITT results

To assess whether a baseline morning ITT cortisol value could be used as a predictor of ITT outcome, ROC curves were generated for ITT results at baseline. Fourteen ITTs occurred in the afternoon and were therefore excluded.

At baseline, a cut-off of ≤390.0 nmol/L resulted in a sensitivity of 100% and specificity of 3.93% (Figure 4B). A cut-off cortisol value of 246.5 nmol/L is achieved at 95% sensitivity (with an associated specificity of 24.89%). A value of 100 nmol/L provided a sensitivity of 44.33% and a specificity of 91.70%.

4 | DISCUSSION

This study provides compelling evidence to confidently lower the current cortisol cut-off from 500 to 416 nmol/L. This maintains a 100.0% test sensitivity whilst achieving an improved specificity of

86.7% (from 43.6%), reducing the number of false positive results from 136 to 32 (76.5% reduction). Use of this cut-off will avoid misdiagnosis of true AI patients, and reduce mislabelling of AI in otherwise healthy patients, with the associated need for glucocorticoid replacement, life-long endocrine follow-up, and persistent suppression of a potentially normal HPA axis. We have also shown that a baseline cortisol of >390 nmol/L can be safely used to exclude AI in our cohort and would have avoided 9 (3%) ITTs from being carried out in non-AI patients. This cut-off value is lower than previously reported, although it is worth noting that previous studies have used less specific assays.[11]

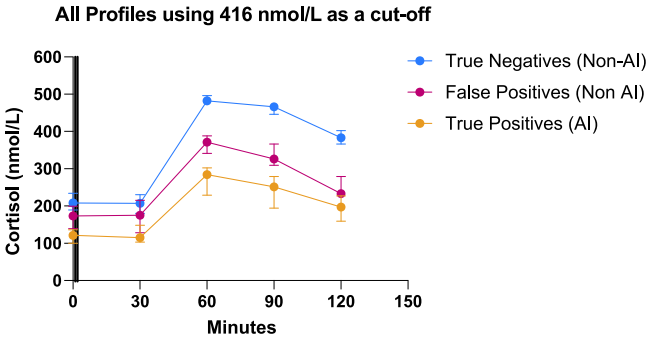

FIGURE 3 ITT Profiles (median cortisol values with 95% CI) according to peak cortisol response using a peak cortisol of 416 nmol/L. True positives: peak cortisol of ≤416 nmol/L and a diagnosis of AI. True negatives: peak cortisol of >416 nmol/L in a healthy individual. False positives: peak cortisol of ≤416 nmol/L in healthy individuals. AI, Adrenal insufficiency; CI, confidence interval; ITT, insulin tolerance test.

Updating the peak cortisol cut-off to ≥416 nmol/L gives an NPV and PPV of 100.0% and 64.8%, respectively. It is important, however, to recognise that the PPV is influenced by disease prevalence and given the rareness of AI, would be expected to remain low. Of note, there were no false negative results within our cohort. This may be due a selection bias in the patients referred for ITT. Patients with an already clear diagnosis of AI (either with a low cortisol postpituitary surgery, or with a previous failed SST result) are started on glucocorticoid replacement and not referred for an ITT.

We reviewed both patients deemed to not have AI, who were well off glucocorticoid replacement therapy and with no evidence of adrenal crises for at least 1 year, and patients who had evidence of persistent AI. The majority of these were due to pituitary disease or following pituitary surgery.

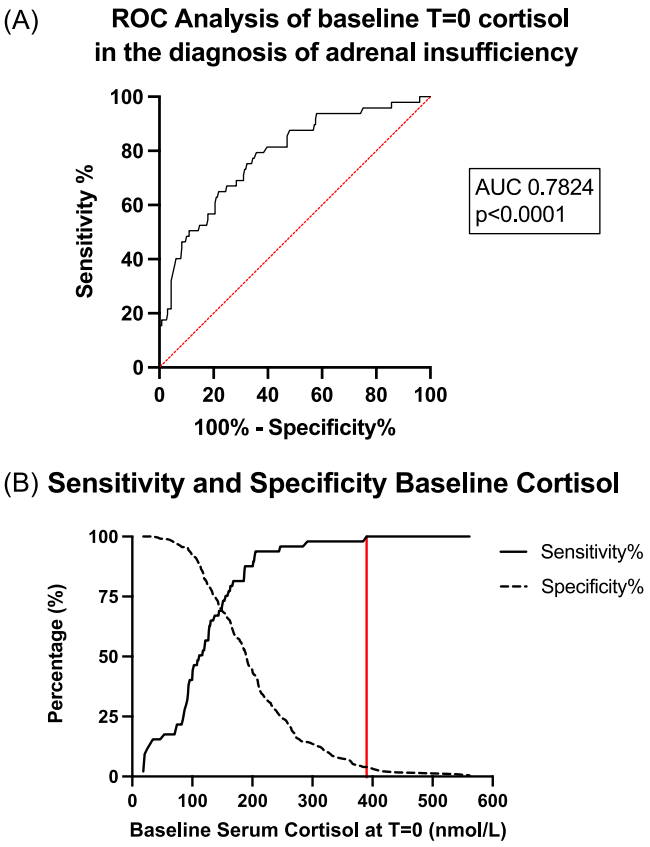

FIGURE 4 (A) ROC Analysis of ITT baseline cortisol values in the diagnosis of adrenal insufficiency. (B) Baseline serum cortisol as a predictor of ITT outcome. Baseline serum cortisol is graphed against the % likelihood of passing (specificity) or failing (sensitivity) the ITT. The red continuous line demarcates the value at which 100% sensitivity is reached. ITT, insulin tolerance test; ROC, receiver operating characteristic.

Although the ITT has traditionally been regarded as the gold standard, it is not without risks, and requires intensive medical and nursing supervision.[12,13] Moreover, it is unpleasant for patients, resource intensive and is contraindicated in patients with ischaemic heart disease, epilepsy, and not advised in children or the elderly.[14]

The SST using conventional high-dose (250 μg) tetrocosactrin has consistently demonstrated good sensitivity and specificity when compared with the ITT in large studies[13,15–17] and has been shown to correlate well with the results of the ITT to exclude clinically secondary AI.[16]

Discrepancies, however, between cortisol responses in both stimulated tests have led to concerns that SST results may be falsely reassuring; with some patients passing the SST but showing suboptimal results on the ITT.[13,18,19] It is also possible that the suboptimal ITT is in fact a false positive. It should be recognised that an incorrect diagnosis of AI made by the ITT is also harmful. The discrepancy is complicated by several factors, including accuracy of the cortisol assays used and inappropriate use of the SST in clinical situations where sensitivity of the HPA axis changes rapidly, for example, recent pituitary surgery (within the preceding 3 weeks).[20] All ITT tests included within this data set were performed at least 6 weeks from surgery.

Interpretation of cortisol cut-off values is further complicated by both the challenge in defining a 'normal' response against healthy individuals and in the differences in assays used.

One study investigating over 200 healthy individuals to define normal thresholds for stimulated serum cortisol levels identified the 95th percentile of peak serum cortisol following an ITT as 408 nmol/L in an Abbott Architect assay as a reference level for healthy volunteers.[21]

It is also worth noting that most of our patients had pituitary disease with accompanying hormone deficiencies (e.g., sex, growth, and thyroid hormone deficiencies). These can affect the concentration of cortisol binding globulin, and the measured total cortisol values may therefore not accurately reflect active cortisol levels.

Historically, cut-off values were defined in normal patients undergoing major surgery and have erred on the side of caution[8] without recognising the harms of glucocorticoid replacement therapy. A study in our centre, using the Abbott assay platform, showed that the peak stress response to major surgery could vary from 375 to 1452 nmol/L[22] and for this reason, our local guidelines have suggested that clinical judgement should be used in any patient with a peak cortisol between 375 and 500 nmol/L before being labelled with AI. This has resulted in a cohort of patients included in this analysis who have been shown to not have AI, but with a peak cortisol response between 375 and 500 nmol/L. Our aim was to reduce the false positive rate in individuals suspected to have an AI diagnosis and we therefore labelled patients who remained well for at least 1 year without glucocorticoid replacement therapy and without adrenal crises, as not AI. In those who have a partial response to the ITT, tapering of glucocorticoid therapy may enable recovery of endogenous cortisol production.[23]

Our results are in keeping with studies evaluating stimulated cortisol responses to synthetic adrenocorticotropin (ACTH) using more specific cortisol assays with resultant lowering of cut-off values.[24,25] Javorsky et al. evaluated basal and stimulated cortisol responses to synacthen using two monoclonal antibody assays and LC-MS/MS compared with a polyclonal antibody assay. They demonstrated a lower threshold for cortisol cut-off values of 14–15 μg/L (386–413 nmol/L) in response to synthetic ACTH using newer LC-MS/MS confirmed with monoclonal assays. They suggested use of the historical cut-off of 18 μg/L (497 nmol/L) would result in twice as many patients being given a biochemical diagnosis of AI.[25]

Our results are reflective of a large well-defined population treated at a tertiary London centre but may not be generalisable to other populations. The analysis of the ITT results was strengthened by use of a single assay to assess cortisol measurement and the longitudinal up to date follow up by a panel of endocrine adrenal specialists, including those with previous radiotherapy treatment. Other studies have been limited by smaller sample sizes, or use of multiple assays to compare cut-off cortisol values, making it difficult to draw accurate conclusions.

5 | LIMITATIONS

The study was limited by the retrospective nature of the data collection and assessment, with the potential for clinician selection bias in classifying patients as having a diagnosis of AI or not. Reviewing clinicians were not blinded to patients' ITT results at the time of classifying patients with a diagnosis.

Forty patients underwent more than one test, which may have introduced additional bias as intra-individual measurements tend to be more similar than measurements taken between individuals, thereby introducing a clustering effect. We are confident this is not the case as repeated tests were only undertaken where a change in circumstances was expected following pituitary surgery or pituitary radiotherapy. These were reviewed as independent tests, albeit from the same individuals.

Inclusion within the study relied on the availability of recent electronic patient records which enabled correct follow-up of patients from the date of their ITT. As a result, data collected from patients without updated records (<12 months) may not have been identified in the study.

The results of this study would benefit from further external prospective validation in other centres using the Abbott platform to assess the generalisability of the results.

6 | CONCLUSION

This study demonstrates that the cortisol cut-off on ITTs measured using Abbott platforms can be safely lowered to 416 nmol/L without compromising test sensitivity. Use of this cut-off value avoids the misdiagnosis of AI and subsequent unnecessary glucocorticoid replacement therapy. The study also highlights the need for further

prospective work to investigate and update assay-specific cortisol cut-offs to avoid the misdiagnosis of AI in an era of more specific immunoassays.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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