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LETTER

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Diagnostic accuracy of morning serum cortisol concentration in predicting secondary adrenal insufficiency

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To the Editor,

Adrenal insufficiency (AI) can be a life-threatening disease, which is why patients at risk of having secondary AI due to pituitary disease and/or its management typically undergo periodic evaluation with dynamic testing. This is typically done with the 250 µg Synacthen stimulation test (SST), which is itself safer, less disagreeable and less resource intensive than the, now superseded, insulin stress test. However, we propose a more rapid, convenient and cost-effective method based on the basal serum cortisol threshold.

Several studies have evaluated the basal serum cortisol concentration as an initial screening test for AI, although no consensus has yet been reached regarding cut-off values.[1,2] Disparities in patient profiles, cortisol assays, and test timing are some of the factors that could explain such divergence. The degree of HPA axis impairment may also vary with contrasting adrenal and pituitary aetiologies. Glucocorticoid use is present in up to 3% of the UK and US populations, which may result, consequently, in hypothalamic-pituitary-adrenal (HPA) axis suppression.[3] This, amidst other pathologies present in a clinical setting, underscores the significance of identifying an unimpaired HPA axis.

As part of routine clinical audit, we undertook a 10-year retrospective analysis of adult patients (≥18 years old) who had undergone SST in our tertiary centre due to being at risk of secondary AI from parasellar lesions, pituitary surgery, or cranial irradiation. AI was defined as a peak serum cortisol level <550 nmol/L (Cortisol-I assay, $N = 284$) or <420 nmol/L (Cortisol-II assay, $N = 311$) by Roche Diagnostics, based on previously validated cut-off values from healthy control population.[4,5] A validated regression equation was used to convert equivalent results from Roche I to Roche II assay,[6] and receiver operating curve (ROC) analysis was used to evaluate diagnostic performance. This analysis included 595 consecutive SSTs performed for this indication between 2010 and 2020, of which 51 (8.6%) led to a diagnosis of AI.

Basal cortisol ROC analysis gave an area under the curve of 0.975 (95% confidence interval [CI]: 0.959–0.986, $p < .0001$). Applying a threshold basal cortisol concentration ≤165 nmol/L, on Roche II assay, for proceeding with SST, would have avoided 503 of these (92%), but 5/51 failed SSTs (9.8%) would have be missed. However, with a threshold cortisol ≤237 nmol/L, no diagnoses of secondary AI would have been missed through failure to proceed to SST (95% CI: 93%–100%) and 399 (73%) would have been avoided (sensitivity 100%; specificity 73.4%) (see Table 1).

Our data are in agreement with previous findings that a carefully selected basal serum cortisol threshold can reliably identify those patients at risk of secondary AI (in whom SST should be performed).[1,2,7] In this way, the requirement for confirmatory dynamic testing with SST could be reduced by up to 30% in our experience. Moreover, Manosroi et al.[7] demonstrated that the timing of basal serum cortisol testing is not critical, allowing for greater test-centre flexibility. In our cohort all patients had SST performed between 8 AM and midday.

These data confirm the reliability of basal cortisol screening in relation to a proportionately small subgroup of "at risk" patients and, therefore, the overall savings in staff costs and consumables remain

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TABLE 1 Youden's *J*-statistic in relation to selected thresholds of basal serum cortisol concentration.

Threshold serum cortisol (nmol/L)	Sensitivity	Specificity	LR+	LR−	PV+	PV−	*J*-Index
≤165	90.2 (78.6–96.7)	92.5 (89.9–94.5)	12.0 (10.9–13.1)	0.11 (0.04–0.3)	52.9 (41.9–63.7)	99.0 (97.7–99.7)	0.827
≤200	96.1 (86.5–99.5)	83.6 (80.3–86.7)	5.9 (5.5–6.3)	0.05 (0.01–0.2)	35.5 (27.6–44.1)	99.6 (98.4–99.9)	0.797
≤215	98.0 (89.6–100)	80.9 (77.3–84.1)	5.1 (4.8–5.4)	0.02 (0.003–0.2)	32.5 (25.2–40.5)	99.8 (98.7–100)	0.789
≤237	100 (93–100)	73.4 (69.4–77.0)	3.8 (3.6–3.9)	0	26.0 (20–32.8)	100 (99.1–100)	0.734

Abbreviations: LR, likelihood ratio; PV, predictive value.

relatively modest in the overall scheme of things. Currently, a proportion of patients being weaned off immunosuppressive glucocorticoid therapy undergo SST, after suspending glucocorticoids for 24 h, to confirm recovery of the HPA axis.[3] If similar basal serum cortisol thresholds could be determined for the increasing number of patients at risk of iatrogenic secondary AI due to glucocorticoids prescribed as disease-modifying agents, then even greater resource savings could be implemented without any adverse impact on patient safety.

In summary, morning serum cortisol testing offers the potential to be a first-step diagnostic method to screen for HPA axis suppression, diminishing the need to perform resource-intensive SSTs in up to 73% of patients with suspected AI. Further studies are needed to validate our proposed threshold values for other cortisol assays and wider patient subgroups.

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REFERENCES

1. Montes-Villarreal J, Perez-Arredondo LA, Rodriguez-Gutierrez R, et al. Serum morning cortisol as a screening test for adrenal insufficiency. *Endocrine Practice*. 2020;26(1):30-35.
2. Struja T, Briner L, Meier A, et al. Diagnostic accuracy of basal cortisol level to predict adrenal insufficiency in cosyntropin testing: results from an observational cohort study with 804 patients. *Endocrine Practice*. 2017;23(8):949-961.
3. Woods CP, Argese N, Chapman M, et al. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. *Eur J Endocrinol*. 2015;173(5):633-642.
4. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM. Defining the normal cortisol response to the short Synacthen test: implications for the investigation of hypothalamic–pituitary disorders. *Clin Endocrinol*. 1998;49:287-292.
5. Javorsky BR, Raff H, Carroll TB, et al. New cutoffs for the biochemical diagnosis of adrenal insufficiency after ACTH stimulation using specific cortisol assays. *J Endocr Soc*. 2021;5:1-11.
6. Vogeser M, Kratzsch J, Ju Bae Y, et al. Multicenter performance evaluation of a second generation cortisol assay. *Clin Chem Lab Med*. 2017;55(6):826-835.
7. Manosroi W, Phimphilai M, Khorana J, Atthakomol P. Diagnostic performance of basal cortisol level at 0900-1300h in adrenal insufficiency. *PLoS One*. 2019;14(11):e0225255.