Diagnostic value of the late-night salivary cortisol in the diagnosis of clinical and subclinical Cushing's syndrome: results of a single-center 7-year experience

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ABSTRACT

Late-night salivary cortisol (LNSaC) is an easy-to-use test reflecting the free cortisol level in the serum and does not require hospitalization. Controlled studies reported that LNSaC has a high sensitivity and specificity, but have not set a clearly defined cut-off value to be used in the diagnosis of Cushing's syndrome. In this study, we aimed to evaluate the diagnostic performance of LNSaC in patients with clinical Cushing's syndrome (CCS) and subclinical Cushing's syndrome (SCS). The data of 543 patients, whose LNSaC levels were assessed using electrochemiluminescence immunoassay method, were retrospectively evaluated. The study included a total of 324 patients: 58 patients with CCS, 53 patients with SCS, and 213 patients without Cushing's syndrome (NoCS). The cause of the Cushing's syndrome was hypophyseal in 26 patients (45%), adrenal in 24 patients (41%), and ectopic in 8 patients (14%) in the CCS group. Median LNSaC levels were 0.724 (0.107–33) µg/dL in CCS group, 0.398 (0.16–1.02) µg/dL in SCS group, and 0.18 (0.043–0.481) µg/dL in NoCS group (p=0.001). Accordingly, LNSaC had 89.6% sensitivity and 81.6% specificity at a cut-off value of 0.288 µg/dL in the diagnosis of CCS; and had 80.7% sensitivity and 85.1% specificity at a cut-off value of 0.273 µg/dL in the diagnosis of SCS. In the present study, a lower sensitivity and specificity than previously reported was found for LNSaC in the diagnosis of CCS. Moreover, the diagnostic performance of LNSaC in patients with SCS was close to its diagnostic performance in patients with CCS. Each center should determine its own cut-off value based on the method adopted for LNSaC measurement, and apply that cut-off value in the diagnosis of Cushing's syndrome.

Significance of this study

What is already known about this subject?

- Late-night salivary cortisol is an easy-to-use test reflecting the free cortisol level in the serum and does not require hospitalization.
- Controlled studies reported that late-night salivary cortisol has a high sensitivity and specificity, but have not set a clearly defined cut-off value to be used in the diagnosis of Cushing's syndrome.

What are the new findings?

- The diagnostic performance of late-night salivary cortisol in patients with subclinical Cushing's syndrome was close to its diagnostic performance in patients with clinical Cushing's syndrome.

How might these results change the focus of research or clinical practice?

- Each center should determine its own cut-off value based on the method adopted for late-night salivary cortisol measurement, and apply that cut-off value in the diagnosis of Cushing's syndrome.

INTRODUCTION

Cushing's syndrome arises due to excessive and long-term exposure to cortisol, has symptoms such as purple striae, proximal muscle weakness and easy bruising, and is characterized by an increase in both morbidity and mortality.[1] Subclinical Cushing's syndrome (SCS), on the other hand, is usually detected in the patients with adrenal incidentaloma (AI) with no clinical symptoms or findings of excess cortisol, but with laboratory findings complying with hypercortisolemia.[2] Cushing's syndrome might be clinically suspected based on the symptoms and findings of the patients, but taking the likelihood of pseudo-Cushing's cases such as obesity, alcoholism and psychiatric disorders into consideration, the definitive diagnosis must be confirmed by the biochemical tests.[1] Currently available biochemical diagnostic tests are 24-hour urinary free cortisol (UFC) test, 1 mg overnight dexamethasone suppression test (DST), 2-day 2 mg DST, late-night serum cortisol (LNSeC), and late-night salivary cortisol (LNSaC), each of which has a different sensitivity and specificity in the diagnosis of Cushing's syndrome.[1]

Patients with Cushing's syndrome are known to have disrupted circadian rhythm of cortisol and the lowest cortisol levels, which should normally be detected at night, are not encountered in these patients.[3] LNSeC and LNSaC can be used in Cushing's syndrome diagnostics, to figure out whether the cortisol circadian rhythm is disrupted. The hospitalization requirement of LNSeC makes it unpractical. LNSaC, on the other hand, is a convenient and cost-effective test reflecting free serum cortisol level that does not require hospitalization and can be performed in an outpatient setting.[4]

LNSaC is among the first-line tests recommended in the diagnosis of Cushing's syndrome, and its use has been increasing over the recent years.[1] However, studies on the performance of LNSaC in the diagnosis of Cushing's syndrome have varying results and thus are lacking of a consensus on the LNSaC cut-off value.[5–10] Various cut-off values and various sensitivity and specificity values for these cut-off values have been reported based on the data collection and laboratory methods and the population the study was conducted on.[5–10] In this retrospective study, we aimed to evaluate the diagnostic performance of LNSaC as measured by electrochemiluminescence immunoassay (ECLIA) method in patients with clinical Cushing's syndrome (CCS) and SCS.

MATERIALS AND METHODS

Data out of 543 patients, whose salivary cortisol levels were measured in Akdeniz University Hospital of School of Medicine, Biochemistry Laboratory, between January 2010 and January 2017, were retrospectively analyzed. The authors obtained the appropriate Institutional Review Board approval/consent as per their institutional policy. Study design is given in figure 1. The study only included adult patients whose LNSaC levels were measured and hypercortisolemia status was analyzed due to the causes such as the suspected Cushing's syndrome, obesity, or AI, at the Department of Endocrinology and Metabolic Diseases. Patients without an LNSaC level measurement were excluded from the study. The study included the patients provided that all the necessary tests for hypercortisolemia were completed and evaluated, and thereupon a definite decision regarding the diagnosis or ruling-out of the CCS or SCS has been established.

Patients who have an additional disorder that may cause pseudo-Cushing's syndrome, such as depression, alcoholism, and pregnancy as well as the patients who are on any medication with an impact on cortisol metabolism, have acute diseases, are using glucocorticoids, are working at the night shift, and those with incomplete or discordant test results were excluded from the study.

A total of 324 patients were included in the study. Based on their test results, the patients were classified into three groups, which are: patients with CCS (58), patients with SCS (53), and patients without Cushing's syndrome (NoCS) (213) (figure 1). Diagnostic workup for Cushing's syndrome comprised cortisol level measurements after 1 mg or 2-day 2 mg DST, LNSaC levels, and 24-hour UFC levels. Cut-off value for the cortisol level after 1 mg or 2-day 2 mg DST was taken as 1.8 µg/dL.[1] Serum sample for LNSeC assessment was collected while the patients were awake and 7.5 µg/dL was accepted as the cut-off value.[1] In the event of a 24-hour UFC level higher than the reference value, the test result was considered positive.[1] Among patients manifesting hypercortisolemia-related symptoms and findings (such as purple striae, proximal muscle weakness, easy bruising), those who are positive for at least 2 of the 3 tests for hypercortisolemia were accepted as Cushing's syndrome.[1] Patients on whom, after being diagnosed with Cushing's syndrome, evaluations towards the etiology of the disease were done and thus a clear etiologic reason is shown were included in the study. Underlying etiologies of the patients with Cushing's syndrome were recorded (adrenocorticotropic hormone (ACTH)-dependent (pituitary and ectopic Cushing's syndrome) and ACTH-independent Cushing's syndrome). The diagnosis of pituitary Cushing's syndrome was made based on the presence of unsuppressed ACTH levels and presence of a pituitary adenoma larger than 5 mm, and in the absence of adenoma, the diagnosis was made based on inferior petrosal sinus sampling. Ectopic Cushing's syndrome diagnosis was considered on the presence of unsuppressed ACTH levels and the absence of an appearance complying with adenoma in the hypophysis and was finalized with bilateral inferior petrosal sinus sampling. Adrenal Cushing's syndrome diagnosis, on the other hand, was made on the presence of suppressed ACTH levels and radiologically proven presence of adrenal mass.

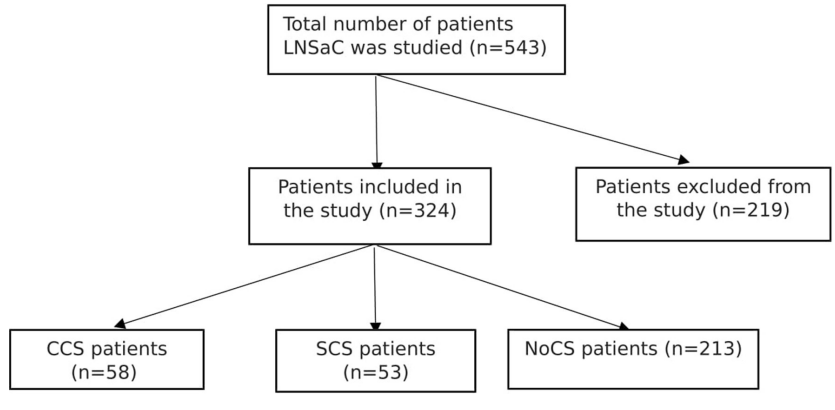

Figure 1 Study design. CCS, clinical Cushing's syndrome; LNSaC, late-night salivary cortisol; NoCS, no Cushing's syndrome; SCS, subclinical Cushing's syndrome.

Patients with adrenal adenoma with high cortisol levels and suppressed ACTH levels after 1 mg DST, with another positive test result complying with hypercortisolemia (high cortisol levels after 2-day 2 mg DST, high levels of 24-hour UFC or high LNSeC levels), but without remarkable hypercortisolemia-related symptoms and findings such as purple striae, proximal muscle weakness, or easy bruising, were accepted as patients with SCS.[11–13]

Patients evaluated due to possible hypercortisolemia but yielded normal test results, and in whom hypercortisolemia was definitely eliminated are taken as the control group (NoCS). Of the patients in the NoCS group, those with an adrenal mass larger than 1 cm as detected in the CT, and those who are shown to be non-functional in terms of Cushing's syndrome, primary hyperaldosteronism and pheochromocytoma trough biochemical tests were accepted as patients with non-functional AI, and these patients (47) were taken as the control group (AI group) for SCS group.

A cylinder-shaped dental cotton roll was used to collect the sample for LNSaC testing and placed into a plastic tube to carry the samples to the laboratory.[10] Saliva sample was collected at 11:00 PM asking the patient to chew the dental roll for 2–3 minutes. The patients were instructed not to eat, smoke, or brush their teeth within the 3 hours prior to the collection of the saliva sample. After the sample was collected and placed into the tube, it was kept at 4°C–8°C in the refrigerator at home and was brought to the laboratory next morning so that the required tests could be carried out. Some of the patients gave their saliva samples while they were staying at the hospital, some when they were at the ambulatory care, and some both during their inpatient stay and outpatient care. The highest level of cortisol was considered in patients who gave more than one LNSaC sample.

Salivary cortisol levels were measured by ECLIA using Cobas E 601 modular immunoassay analyzer (Roche Diagnostics, Mannheim, Germany). Intra-assay precision of salivary cortisol assays was 3.9% and 2.2%, intermediate precision of assay was 4.9% and 3.4% in concentrations of 0.355 and 1.03 µg/dL, respectively. Measuring range of the assay was 0.054–63.4 µg/dL. The Elecsys Cortisol II assay has been standardized against the reference materials (IRMM/IFCC-451 panel) which were value assigned by the reference measurement procedure (isotope dilution-gas chromatography/mass spectrometry). The Roche Elecsys Cortisol II assay's cross-reactivity with cortisone was 6.58%.

Serum cortisol was measured by ECLIA using Cobas E 601 modular immunoassay analyzer (Roche Diagnostics). Intra-assay and interassay coefficients of variations (CV) of the cortisol kit were 1.7% (control value: 4.69±0.08 µg/dL) and 2.2% (control value: 4.51±0.10 µg/dL), respectively. Minimal detectable serum cortisol level was 0.018 µg/dL and measuring range of the assay was 0.018–63.4 µg/dL.

UFC was measured by ECLIA using Cobas E 601 modular immunoassay analyzer (Roche Diagnostics). Intra-assay and interassay CVs for the kit were 2.9% (control value: 41.9±1.20 µg/dL) and 2.5% (control value: 42.1±1.04 µg/dL), respectively.

Table 1 Basic clinical data of the patients

	CCS (n=58)	SCS (n=53)	NoCS (n=213)	p Values
Age (y)	48±12.7	58.7±10.5	47.2±15.4	0.001*
Gender				
Male, n (%)	12 (20.7)	11 (20.8)	62 (29.1)	0.265
Female, n (%)	46 (79.3)	42 (79.2)	151 (70.9)	
Diabetes mellitus, n (%)	31 (53.4)	18 (34)	83 (39)	0.076
Hypertension, n (%)	38 (65.5)	29 (54.7)	82 (38.5)	0.001†
Obesity, n (%)	20 (35.1)	5 (9.4)	81 (38.1)	0.003‡
Coronary artery disease, n (%)	7 (12.3)	4 (7.7)	21 (9.9)	0.72
Malignancy, n (%)	2 (3.5)	3 (5.7)	15 (7)	0.6
Osteoporosis, n (%)	6 (10.5)	3 (5.7)	5 (2.3)	0.02§
Hyperlipidemia, n (%)	22 (38.6)	16 (30.2)	64 (30)	0.45

*NoCS versus SCS, p=0.001; CCS versus SCS, p=0.001.
†NoCS versus CCS, p=0.001; NoCS versus SCS, p=0.024.
‡NoCS versus SCS, p=0.001; CCS versus SCS, p=0.001.
§NoCS versus CCS, p=0.013.
CCS, clinical Cushing's syndrome; NoCS, no Cushing's syndrome; SCS, subclinical Cushing's syndrome.

Statistical analysis

Data were analyzed in SPSS V.21 package program. Nominal data were presented as frequency (percentage); ordinal data and continuous variables were shown as either mean±SD or median (minimum-maximum), depending on normal distribution. To study the intergroup differences of categorical variables, X^2 tests were applied. Continuous variables were evaluated using Mann-Whitney U test or independent sample t-test for independent variables in pairwise comparison of subgroups, and Kruskal-Wallis tests in multiple subgroup analyses. For statistical significance, p value was taken as 0.05.

RESULTS

The reason to order an LNSaC test was the suspected Cushing's syndrome in 124 patients (38%), AI in 111 patients (34%), obesity in 48 patients (15%), and other causes such as persistent hypertension and osteoporosis in 41 patients (13%). In CCS group, Cushing's syndrome was hypophyseal in 26 patients (45%), adrenal in 24 patients (41%), and ectopic in 8 patients (14%).

The basic clinical data and laboratory findings of the patients are given in tables 1–3. Median LNSaC levels were 0.18 (0.043–0.481) µg/dL in NoCS group, 0.724 (0.107–33) µg/dL in CCS group, 0.398 (0.16–1.02) µg/dL in SCS group, and 0.141 (0.05–0.367) µg/dL in AI group, and a statistically significant difference was detected between the 3 groups (p=0.001) (tables 2 and 3).

In patients with CCS, the cut-off value of 0.108 µg/dL had a high sensitivity (98.2%) but a very low specificity (22.5%). Again in patients with CCS, the cut-off value of 0.432 µg/dL had a high specificity (98.1%) but the sensitivity was relatively low (72.4%). The cut-off value of 0.288 µg/dL for patients with CCS had the optimal sensitivity (89.6%) and specificity (81.6%) (table 4).

In patients with SCS, the cut-off value of 0.161 µg/dL had a high sensitivity (96.1%) but a very low specificity (57.4%). In patients with SCS, the cut-off value of 0.342 µg/dL had a high specificity (97.8%) but a relatively

Table 2 Laboratory test results of the patients*

	CCS (n=58)	SCS (n=53)	NoCS (n=213)	p Values
LNSaC (µg/dL)	0.724 (0.107–33)	0.398 (0.16–1.02)	0.18 (0.043–0.481)	0.001†
Basal cortisol (µg/dL)	23.6 (11.9–63)	12.2 (9.6–31.5)	15.2 (5.6–35)	0.001‡
1 mg DST (µg/dL)	13.75 (1.9–63)	3.34 (1.89–18.3)	0.93 (0.26–8.6)	0.001†
2 d 2 mg DST (µg/dL)	8.8 (1.97–63)	2.61 (1.57–13)	1.2 (0.05–2.3)	0.001†
Urinary cortisol (nmol/24 h)	387 (16–1468)	121.5 (11–289)	56 (5–230)	0.001†
LNSeC (µg/dL)	20 (4.7–63)	8.77 (3.9–24.42)	3.86 (0.9–7.4)	0.001†
ACTH (pg/mL)	26 (1–511)	4 (1–9)	19 (1–84)	0.001§
Glucose (mg/dL)	106 (69–331)	95 (65–337)	97 (64–593)	0.41
ALT (IU/L)	24 (10–183)	16 (6–35)	19 (5–105)	0.001¶
Creatinine (mg/dL)	0.68 (0.4–1.5)	0.68 (0.43–1.9)	0.71 (0.4–2.5)	0.23
Total cholesterol (mg/dL)	217.6±53.5	209.6±59.9	192.4±48.5	0.035**
LDL-cholesterol (mg/dL)	133.4±38.5	127.6±41	120.6±39.8	0.171
HDL-cholesterol (mg/dL)	46 (24–91)	48 (32–98)	42 (13–92)	0.09
Triglyceride (mg/dL)	137 (70–1208)	139 (45–453)	123 (42–629)	0.11
HbA1C (%)	6.5 (4.5–11.2)	5.7 (4.5–9.9)	5.8 (4.6–17.7)	0.038

*Normally distributed variables are shown as mean±SD; variables without normal distribution are shown as median (minimum-maximum).
†NoCS versus CCS, p=0.001; NoCS versus SCS, p=0.001; CCS versus SCS, p=0.001.
‡NoCS versus CCS, p=0.001; CCS versus SCS, p=0.001.
§NoCS versus SCS, p=0.001; CCS versus SCS, p=0.001.
¶NoCS versus CCS, p=0.007; NoCS versus SCS, p=0.014; CCS versus SCS, p=0.001.
**NoCS versus CCS, p=0.037.
ACTH, adrenocorticotropic hormone; ALT, alanine aminotransferase; CCS, clinical Cushing's syndrome; DST, dexamethasone suppression test; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LNSaC, late-night salivary cortisol; LNSeC, late-night serum cortisol; NoCS, no Cushing's syndrome; SCS, subclinical Cushing's syndrome.

low sensitivity (63.4%). In patients with SCS, the cut-off value of 0.273 µg/dL had the optimal sensitivity (80.7%) and specificity (85.1%) (table 4). Figure 2 plots the receiver operating characteristic (ROC) curves for LNSaC in patients with CCS and SCS.

DISCUSSION

LNSaC is among the first-line tests recommended in the diagnosis of Cushing's syndrome, and its use has been increasing over the recent years.[1] However, studies on the performance of LNSaC in the diagnosis of Cushing's syndrome have varying results. For LNSaC, different sensitivity and specificity values for corresponding different cut-off values have been reported and there is no consensus on what should be the cut-off value.[5–10] Based on our results, 0.288 µg/dL cut-off value measured by ECLIA for LNSaC had 89.6% sensitivity and 81.6% specificity in patients with CCS, and 0.273 µg/dL cut-off value had 80.7% sensitivity and 85.1% specificity in patients with SCS. In the previous controlled studies, although the recommended cut-off values depend on the data collection method, the cohort included in the study, diagnostic criteria, and the method of LNSaC measurement, LNSaC has usually been reported to have a high sensitivity and specificity in the diagnosis of Cushing's syndrome.[5 14–16] In a meta-analysis study, 92% sensitivity and 96% specificity was concluded for LNSaC in the diagnosis of Cushing's syndrome.[17]

Table 3 Data from the SCS and AI groups*

	SCS group (n=53)	AI group (n=47)	p Values
LNSaC (µg/dL)	0.398 (0.16–1.02)	0.141 (0.05–0.367)	0.001
Basal cortisol (µg/dL)	17.54±4.9	16.21±5.14	0.245
1 mg DST (µg/dL)	3.19 (1.89–18.3)	1.49 (0.45–8.6)	0.001
ACTH (pg/mL)	4 (1–9)	15 (1–43)	0.001

*Normally distributed variables are shown as mean±SD; variables without normal distribution are shown as median (minimum-maximum).
ACTH, adrenocorticotropic hormone; AI, adrenal incidentaloma; DST, dexamethasone suppression test; LNSaC, late-night salivary cortisol; SCS, subclinical Cushing's syndrome.

While studies suggest significantly high sensitivity and specificity in the diagnosis of Cushing's syndrome, diagnostic performance of LNSaC in the clinical practice may be dissimilar. Our study evaluates the performance of LNSaC in the diagnosis of Cushing's syndrome in the clinical practice. The control group in our study included the healthy individuals and the patients with obesity and non-functional adrenal adenoma, who, in the clinical practice, need exclusion of Cushing's syndrome. Almost all of the previous studies were performed under controlled conditions and are not representative of diagnostic performance of the salivary cortisol in daily clinical practice. In the study by Erickson *et al*, which retrospectively evaluates the data from the Mayo Clinic, 74.5% sensitivity and 90.1% specificity was reported for LNSaC at the cut-off value of 2.8 nmol/L (0.10 µg/dL) in the diagnosis of Cushing's syndrome.[9] In the same study, which measured LNSaC with liquid chromatography/tandem mass spectrometry method, the optimal sensitivity and specificity values determined by ROC analysis at the cut-off value of 2.1 nmol/L (0.076 µg/dL) were 83% and 84.2%, respectively. In our study, although another measurement method, ECLIA, was used, we found similar sensitivity and specificity figures at the cut-off value of 0.288 µg/dL. The study by Erickson *et al* and our study similarly evaluate the diagnostic performance of salivary cortisol in clinical practice, and compared

Table 4 Diagnostic performance of LNSaC at different cut-off values in patients with CCS and SCS

	Value	Sensitivity (95% CI)	Specificity (95% CI)	Likelihood ratio
High sensitivity cut-off for CCS	>0.108	98.2 (90.7 to 99.9)	22.5 (17.1 to 28.7)	1.269
High specificity cut-off for CCS	>0.432	72.4 (59.1 to 83.3)	98.1 (95.2 to 99.4)	38.56
Optimal cut-off for CCS	>0.288	89.6 (78.8 to 96.1)	81.6 (75.8 to 86.6)	4.897
High sensitivity cut-off for SCS	>0.161	96.1 (86.7 to 99.5)	57.4 (42.1 to 71.7)	2.26
High specificity cut-off for SCS	>0.342	63.4 (48.9 to 76.3)	97.8 (88.7 to 99.9)	29.83
Optimal cut-off for SCS	>0.273	80.7 (67.4 to 90.3)	85.1 (71.6 to 93.8)	5.42

CCS, clinical Cushing's syndrome; LNSaC, late-night salivary cortisol; SCS, subclinical Cushing's syndrome.

with the studies performed under controlled conditions, both mention lower sensitivity and specificity values. Although quite high sensitivity and specificity values have been reported in controlled studies, altogether these results suggest that LNSaC has a lower diagnostic performance than expected in the daily clinical practice.

The method used in the measurement was shown to have an effect on the cut-off value of LNSaC.[5] In the previous studies performed using ECLIA method, which is also the method used in our study, at cut-off values ranging between 4 and 10 nmol/L (0.14–0.36 µg/dL), sensitivity values vary between 84.4% and 100% and specificity values vary between 81.1% and 97.9%.[4 5 18–20] In general, the studies report substantially high sensitivity and specificity values, although there are also controlled studies that reported lower sensitivity and specificity values similar to the values observed in our study.[18–20] Different sensitivity and specificity values mentioned in the studies may arise from the study design, characteristics of the patient population included in the study, diagnostic criteria, and the accepted cut-off value.

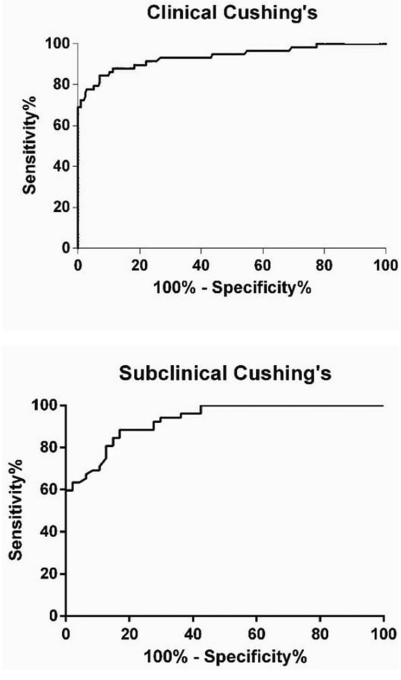

Figure 2 Receiver operating characteristic (ROC) curves for late-night salivary cortisol (LNSaC) in patients with subclinical Cushing's syndrome (SCS) and clinical Cushing's syndrome (CCS).

In majority, sensitivity and specificity of LNSaC in detecting SCS is lower than its sensitivity and specificity in detecting CCS.[7 15 21 22] Kuzu *et al* have shown that LNSaC has 82% sensitivity and 60% specificity in detecting SCS at a cut-off value of 0.18 µg/dL in patients with AI.[23] In our study, we found that at a cut-off value of 0.273 µg/dL, LNSaC has 80.7% sensitivity and 85.1% specificity in the diagnosis of SCS. The cut-off values we determined for the diagnosis of SCS and CCS are close, with an acceptable sensitivity and specificity for both the SCS and CCS diagnosis. Our results imply a comparable performance of LNSaC in the diagnosis of SCS and in the diagnosis of CCS. This suggests that LNSaC can, as is the case in CCS, be used in the diagnosis of SCS and similar cut-off values can be used for both entities.

LNSaC in general is a practical, simple test with a high sensitivity and specificity and is recommended as a first-line test in the diagnosis of Cushing's syndrome. However, there are no clearly defined cut-off values for LNSaC to be used in the diagnosis of Cushing's syndrome. Therefore, in order to correctly use this test, which was reported to have a high sensitivity and specificity value in the controlled studies, each center should establish their own cut-off value depending on their in-house measurement method and then apply such values to decide on the diagnosis. Nevertheless, it should be noted that the diagnostic performance of LNSaC in the clinical practice is likely to be lower than the performance reported in controlled studies. For that reason, in the event of an LNSaC value smaller than the determined cut-off value, and an ongoing suspicion of Cushing's syndrome, the patients must be evaluated with other tests such as DST or 24-hour urine cortisol, as necessary.

Contributors NY, RS: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. GT, HB, SÖ: substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. HAA, MKB: drafting the work or revising it critically for important intellectual content.

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