

THE USEFULNESS OF COMBINED ANALYSIS OF SERUM AND SALIVARY MAXIMUM CORTISOL RESPONSE TO LOW-DOSE ACTH TEST TO DEFINE THE REQUIREMENT OF HORMONE REPLACEMENT TREATMENT



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Introduction

The diagnosis of central adrenal insufficiency (CAI), a life-threatening disorder, is challenging because of its unspecific clinical signs and the limitations of diagnostic tests of adrenal reserve.

The ACTH test in its two versions, the high-dose (250 µg) ACTH test (HDT) and the low-dose (1 µg) ACTH test (LDT), are the most commonly used stimulation tests owing to their safety and good correlation with the gold standard Insulin Tolerance Test (ITT).

According to the reported cut-off value after ACTH stimulation, levels < 18 µg/dl define adrenal insufficiency. (1,2)

However, the serum total cortisol (TC) cut-off value is controversial and a large number of patients are considered to fall into a gray area between 14.5 and 18 µg/dl (3).

Therefore, a risk of overdiagnosis might occur, leading to unnecessary hormone replacement therapy. (3)

Salivary cortisol (SC) is mostly found in the free form (non-bound serum protein fraction) (FC) and its measurement correlates well with both serum TC and FC levels. (4,5)

Objective

The aim of this study was to define a new LDT cut-off value of serum cortisol in pediatric patients suspected of having CAI.

Study design

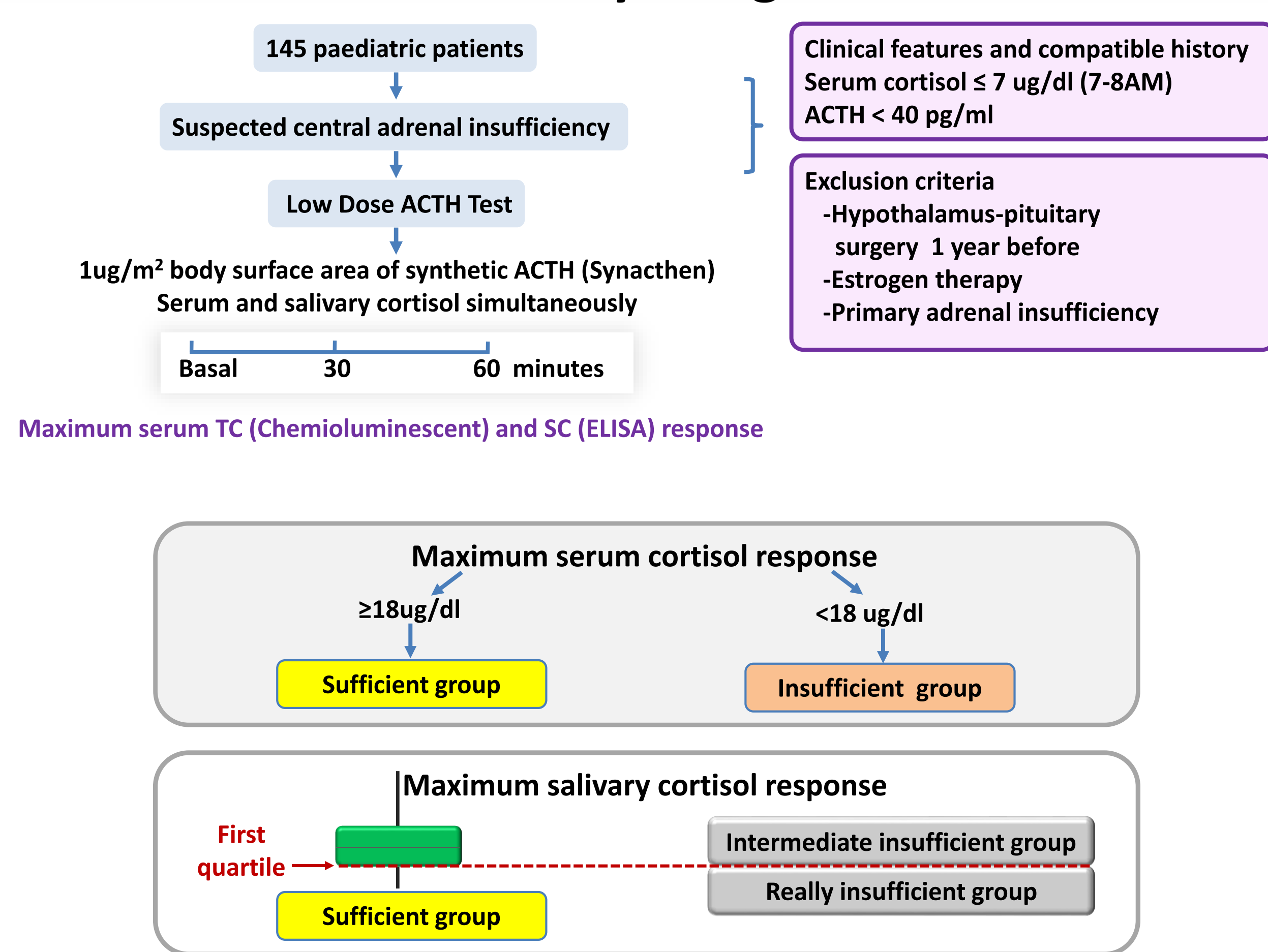
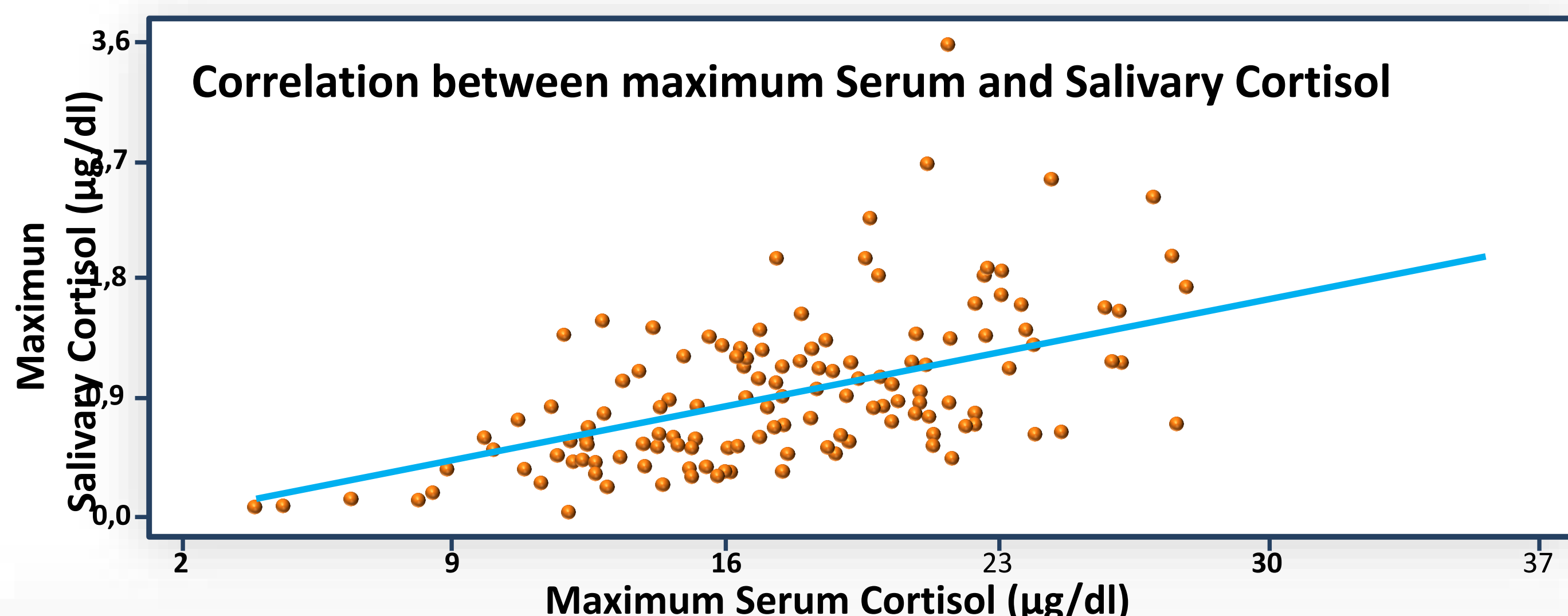


Table 1 Features of 145 patients included in the study

Age (mean, DS) year	11.3±(4.8)
Sex Male n	88*
Female n	57
Tanner pubertal status n (%)	
Prepuberal	59 (40.7)
Puberal	86 (59.3)**
Diagnosis	
Chronic corticoid treatment n (%)	18 (12.4)
Multiple pituitary insufficiency. n(%) secondary to CNT. idiopathic hypopituitarism. SOD, CNS malformation	79 (54.4)
Miscellaneous: PWS, autoimmune disease, Genetic syndromes n(%)	48 (33.1)

* p<0.01
** p<0.01

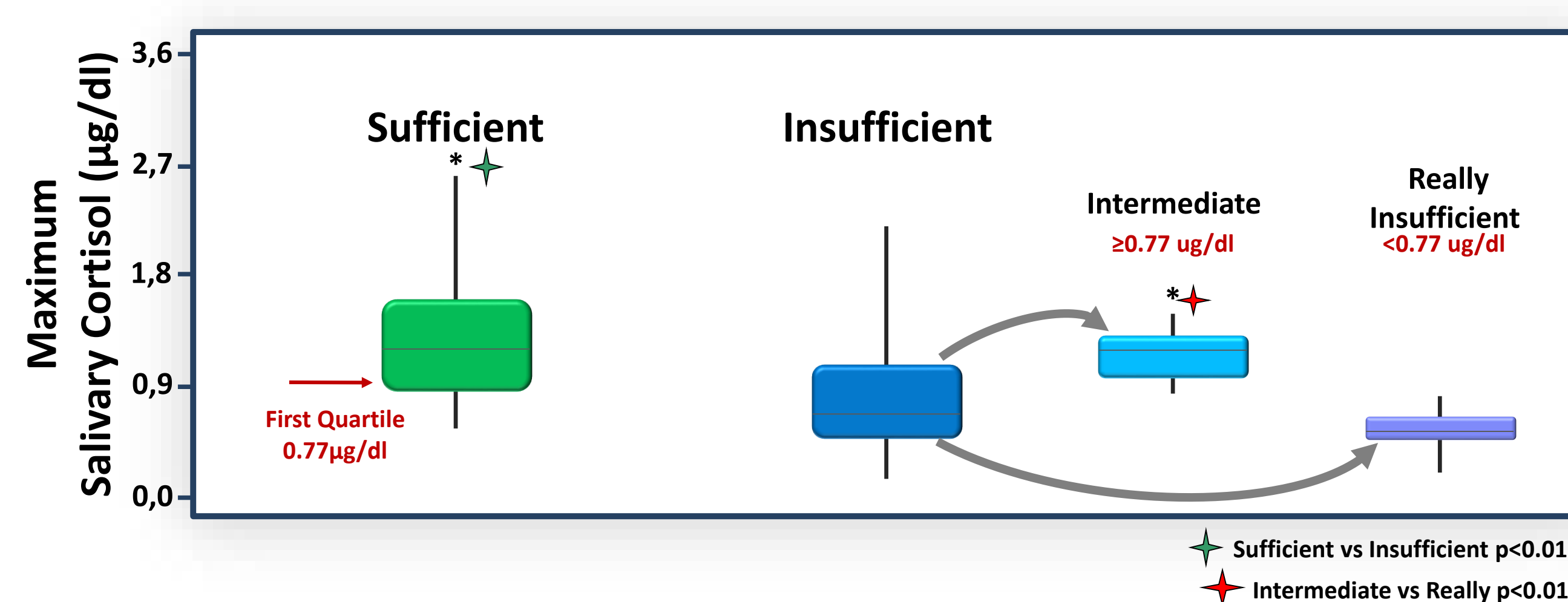
CNT : central nervous tumor, SOD: septo-optic displasia CNS: central nervous system, PWS: Prader Willi Syndrome



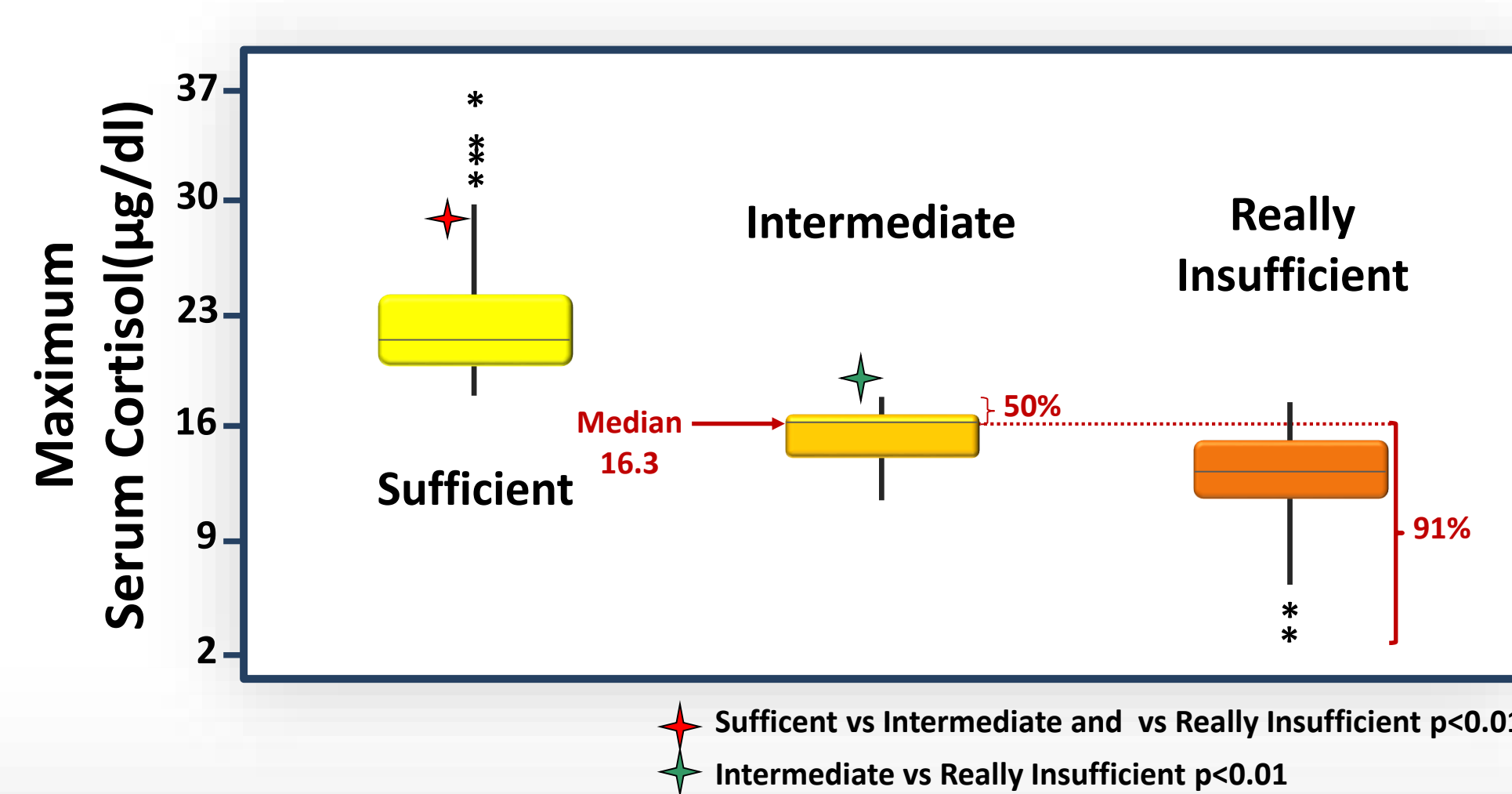
Results

	Adrenal Sufficient response (AS)	Adrenal Insufficient response (AI)		
		total	Intermediate AI	Really AI
n	72	73	28	45
Age mean, (DS) years	10.4(5.5)	12.2 (4)	11.9 (3.1)	12.4 (4.4)
Sex Male n	40	48	18 (37.5%)	30 (62.5%)
Female n	32	25	10 (25%)	15(60%)
Tanner pubertal status n				
Prepubertal	37	22	9 (40.9%)	13 (59%)
Pubertal	35	51	19 (37.2%)	32 (62%)
LDT cortisol maximum (median; interquartile range) µg/dl	21.3 19.8-35.2	14.5 12.2-16.4	16.35 14.2-16.8	13.2 11.3-15.3
LDT maximum salivary cortisol (median; interquartile range) µg/dl	1.14 0.77-1.58	0.58 0.36-1.04	1.16 0.88-1.29	0.41 0.32-0.55

Maximum Salivary cortisol by groups



Maximum Serum cortisol by groups



Summary Results

- 72/145 patients had AS response
- 73/145 patients had AI response
- 91% of patients in Really AI Gr had maximum serum cortisol lower than 16.35 µg/dl.
- 50% in intermediate Gr had maximum serum cortisol greater than 16.35 µg/dl and are probably sufficient responders .

Discordant Results

- 4/45 patients (8.8%) in the Really AI Gr had serum cortisol greater than 16.35 µg/dl
- 17/72 patients (23.6%) in AS Gr had salivary cortisol lower than 0.77 µg/dl
- 14/28 patients (50%) in the Intermediate AI Gr had serum cortisol lower than 16.35µg/dl with salivary cortisol ≥ 0.77 µg/dl

Methods

Serum Cortisol was measured by Immulite 2000 Chemiluminescent . Intra-assay CV were for level 1(3.74 µg/dl) = 6% and level 2 (19.63µg/dl) :3.9% Interassay CV for level 1= 6.9% level 2 = 4.2% Salivary cortisol was measure using enzyme immunoassay (ELISA) Euroimmun. Intra-assay CV were for level 1 (0.2µg/dl) : 4.2% and level 2 (1.3 µg/dl): 3.2% ; Interassay CV for level1: 7.9% and for level2: 4.7%

References

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Conclusion

This suggested cut-off, results in the recognition of an intermediate group and allows avoiding unnecessary hormonal replacement therapy.

However, a rigorous patient follow-up is required, specially in discordant results.

The combined evaluation of maximum serum and salivary cortisol responses improves the accuracy for CAI diagnosis in this paediatric population.

