

Evaluation of The Glucocorticoid, Mineralocorticoid, And Adrenal Androgen Secretion Dynamics in a Large Cohort of Patients Aged 6-18 Years With Transfusion-Dependent B-Thalassemia Major, With An Emphasis on The Impact of Cardiac Iron Load

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Declaration of interest: None

Background: The variable presence of adrenal insufficiency (AI) due to hypocortisolemia (HC) in patients with thalassemia is well established; however, the prevalence of adrenocortical hypofunction (ACH) in the zona glomerulosa and zona reticularis of the adrenal cortex is unknown

Objective and Hypotheses: To establish the prevalence of ACH, we examined the cortisol response to 1 µg- and 250 µg- ACTH tests, plasma aldosterone (A)/plasma renin activity (PRA) ratio, and serum dehydroepiandrosterone sulfate (DHEAS) levels in a large cohort of patients with thalassemia, and to investigate the impact of total body iron load (TBIL) on adrenocortical function

Method: One hundred twenty-one (52 females) patients with β-thalassemia major (β-TM) and 72 healthy peers (38 females) were enrolled. The patients underwent a 250-µg cosyntropin test if their peak cortisol was <500 nmol/L in a 1-µg cosyntropin test. Magnetic resonance imaging (MRI) was performed to assess the MRI based liver iron content and cardiac MRI T2* iron. The associations between ACH and TBIL were investigated.

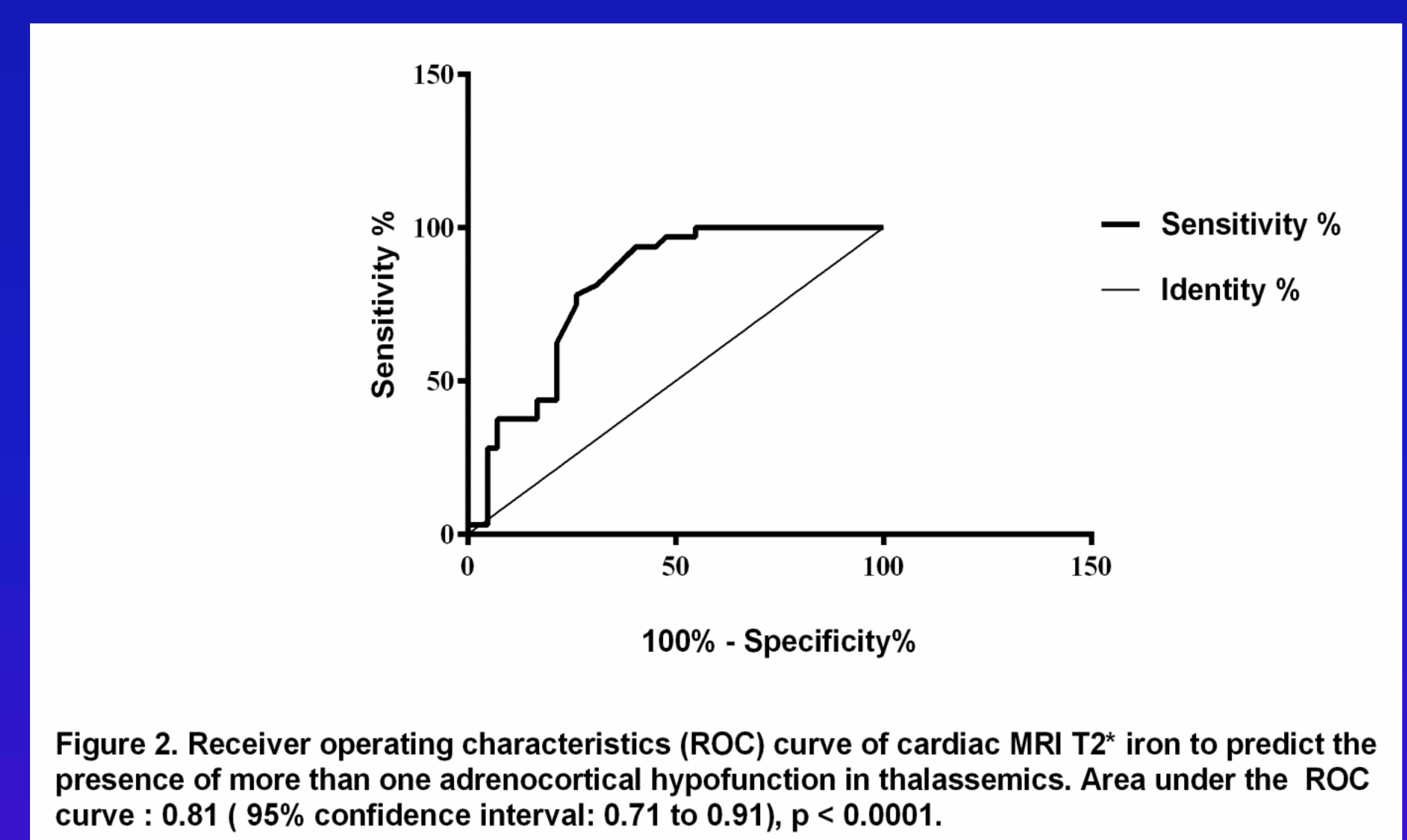
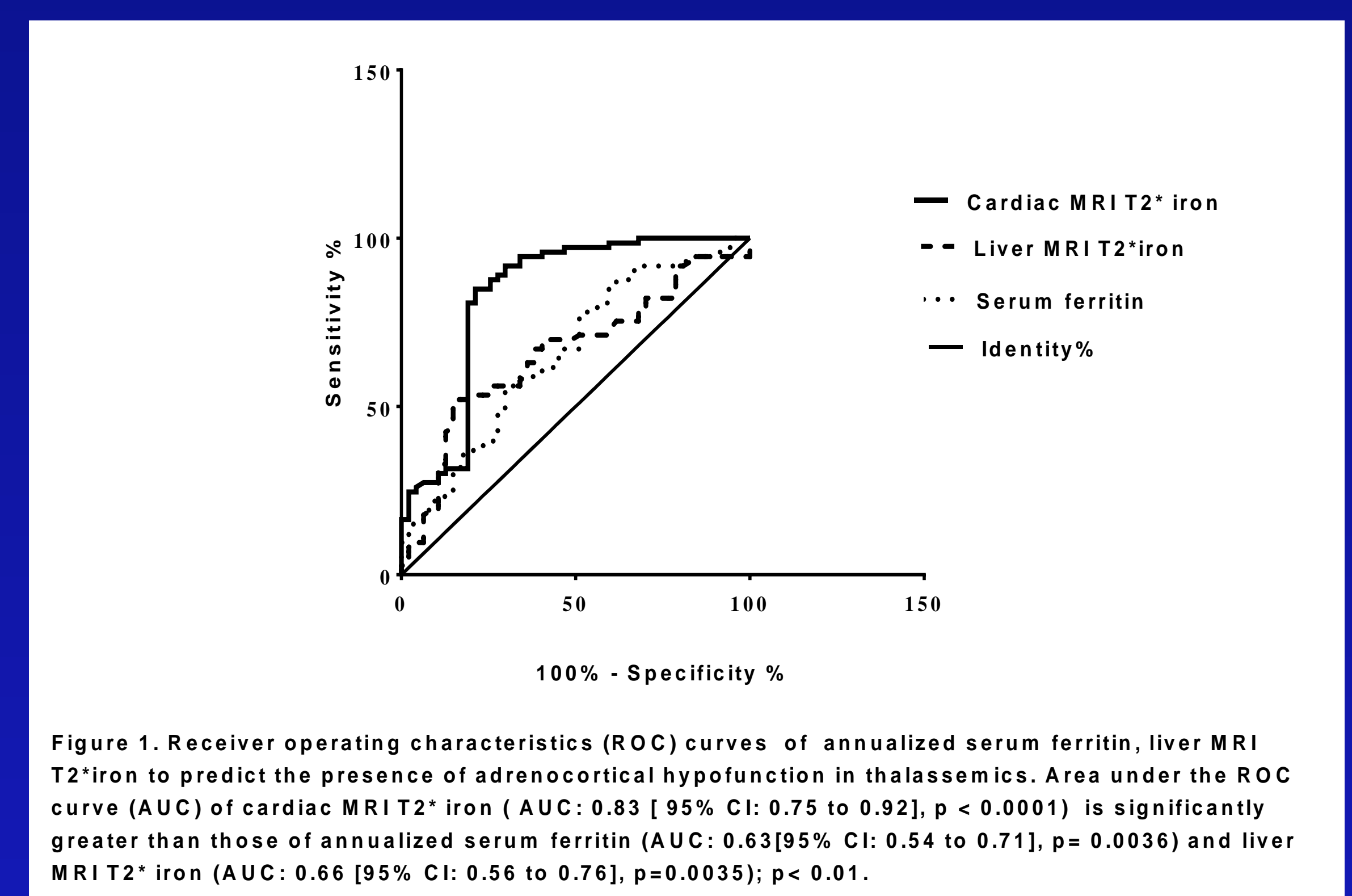
Results: The patients with thalassemia had lower body mass index, Tanner's pubertal staging and diastolic blood pressure than controls (p<0.01). The patients also had lower ACTH, cortisol, DHEAS, and A/PRA values compared with the controls (p<0.001) (Table 1).

Table 1. Biochemical and hormonal evaluation of 121 patients with transfusion dependent beta-thalassemia major and 72 healthy controls

	Patients	Controls	p
Sodium, meq/l	137.5 (137.1 to 137.9)	138.6 (138.2 to 139.0)	0.09
Potassium, meq/l	4.4 [4.1 to 4.9]	4.1[4.0 to 4.7]	0.82
Corticotropin (ACTH), pg/ml	19.0 [12.3 to 26.7]	25.5 [18.0 to 36.7]	<0.0001**
Cortisol _{adjusted} , * µg/dl	10.9 (10.3 to 11.5)	12.7 (11.9 to 13.5)	<0.0001**
Dehydroepiandrosterone sulfate(DHEAS), µg/dl	24.0 [2.3-48.8]	71.0 [17.3 to 148.3]	<0.0001**
DHEAS SDS [†]	-1.8[-2.3 to -1.4]	-0.4[-1.2 to 0.6]	<0.0001**
Aldosterone, ng/dl	8.1 (7.3 to 8.7)	9.0 (8.0 to 9.9)	0.09
Plasma renin activity (PRA), ng/ml/hour	4.9 [3.1 to 6.7]	2.9 [1.9 to 3.9]	<0.0001**
Aldosterone/PRA	1.6 [1.1 to 2.3]	3.2 [2.1 to 4.4]	<0.0001**
FeNa	0.69 [0.58 to 0.81]	0.66 [0.56 to 0.78]	0.63

To convert corticotropin(ACTH) from pg/ml to pmol/l, multiply X 0.22. To convert cortisol from µg/dl to pmol/l, multiply X 27.743. To convert dehydroepiandrosterone sulfate from µg/dl to mcmol/l, multiply X 0.027. To convert Aldosterone from ng/dl to nmol/l, multiply X 0.0277. To convert PRA from ng/ml per hour to µg/l per hour multiply X 1.*The estimated means after adjustment for Tanner's pubertal staging were presented.**p <0.01 is significant. // standard deviation score

Thirty-nine patients (32.2%) had HC [primary (n=1), central (n=36), combined (n=2)], and 47 (38.8%) patients had reduced DHEAS levels; 29 (24.0%) patients had reduced A/PRA ratios. Forty-six (38.0%) patients had hypofunction in one of the adrenal zones, 26 (21.5%) had hypofunction in two adrenal zones, and 9 (7.4%) had hypofunction in all three zones. Patient age and TBIL surrogates were significant independent parameters associated with ACH. The ROC curve analysis revealed that the annualized serum ferritin, LIC, and cardiac MRI T2* iron levels predicted the presence of ACH in patients with thalassemia (Figure 1).



Cardiac MRI T2* iron was the only significant parameter that predicted the severity of ACH at a cut-off of 20.6 ms, with 81% sensitivity and 78% specificity (Figure 2).

Conclusions: Patients with thalassemia have a high prevalence of AI due to HC and zona glomerulosa and zona reticularis hypofunction. TBIL surrogates can predict ACH, but cardiac iron was the only surrogate that was adequately sensitive to predict the severity of ACH.

Note: This study has recently been accepted for publication in Endocrine .