

# The Diagnostic Value of Serum Acid-labile Subunit (ALS) Alone and in Combination with IGF-1 and IGFBP-3 in the Diagnosis of Idiopathic Growth Hormone Deficiency (iGHD)

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## Introduction and Objectives

The acid-labile subunit (ALS) is the crucial third player in the tertiary complex for its function of prolonging the half-life of the IGF-1-IGFBP-3 binary complexes. IGF-1 and IGFBP-3 are routinely determined during the diagnostic work-up for growth hormone deficiency (GHD). The aim of the study is to evaluate the relevance of serum ALS as an additional biomarker, alone or in combination with IGF-1 and IGFBP-3, in the diagnosis of GHD.

## Methods:

In a retrospective study, we had selected 91 children and adolescents (62 males) undergoing standard diagnostic work-up at the Department of Pediatrics and Adolescent Medicine of the Vienna General Hospital from 2010 and 2017. All patients met the inclusion criteria: short stature according to the SOP (height < -2.5 SDS, height deflection > 1 SDS, delta target height > 1.6 SDS), IGF-1 and IGFBP-3 lower than -2 SDS at first presentation, with at least one growth hormone (GH) stimulation tests and available baseline IGF-1, IGFBP-3 and ALS measurements. Patients with brain tumors, small for gestational age, disproportion, coeliac disease, hypothyroidism, syndromes or other pituitary hormones deficiencies, as well as those with no available baseline IGF-1, IGFBP-3 and ALS were excluded. Measurement of IGF-1 was performed using commercial ELISAs (IGF-I E20 Assay, Mediagnost, Germany and ISYS Assay after 2014) which both use the IGF-I standard (WHO NIBSC 02/254). The measurement of IGFBP-3 (IGF-I E20 Assay, Mediagnost, Germany and ISYS Assay after 2014) uses the same "sandwich principle", with high-specificity and affinity antibodies. For the measurement of ALS we used the commercial ELISA (ALS E35 Assay, Mediagnost, Germany). Statistical analysis of different models consisting of ROC for various combinations of the measured parameters, as well as Odds ratio calculations were conducted using SAS software. 7 ng/ml was the cut off defining biochemical GH deficiency.

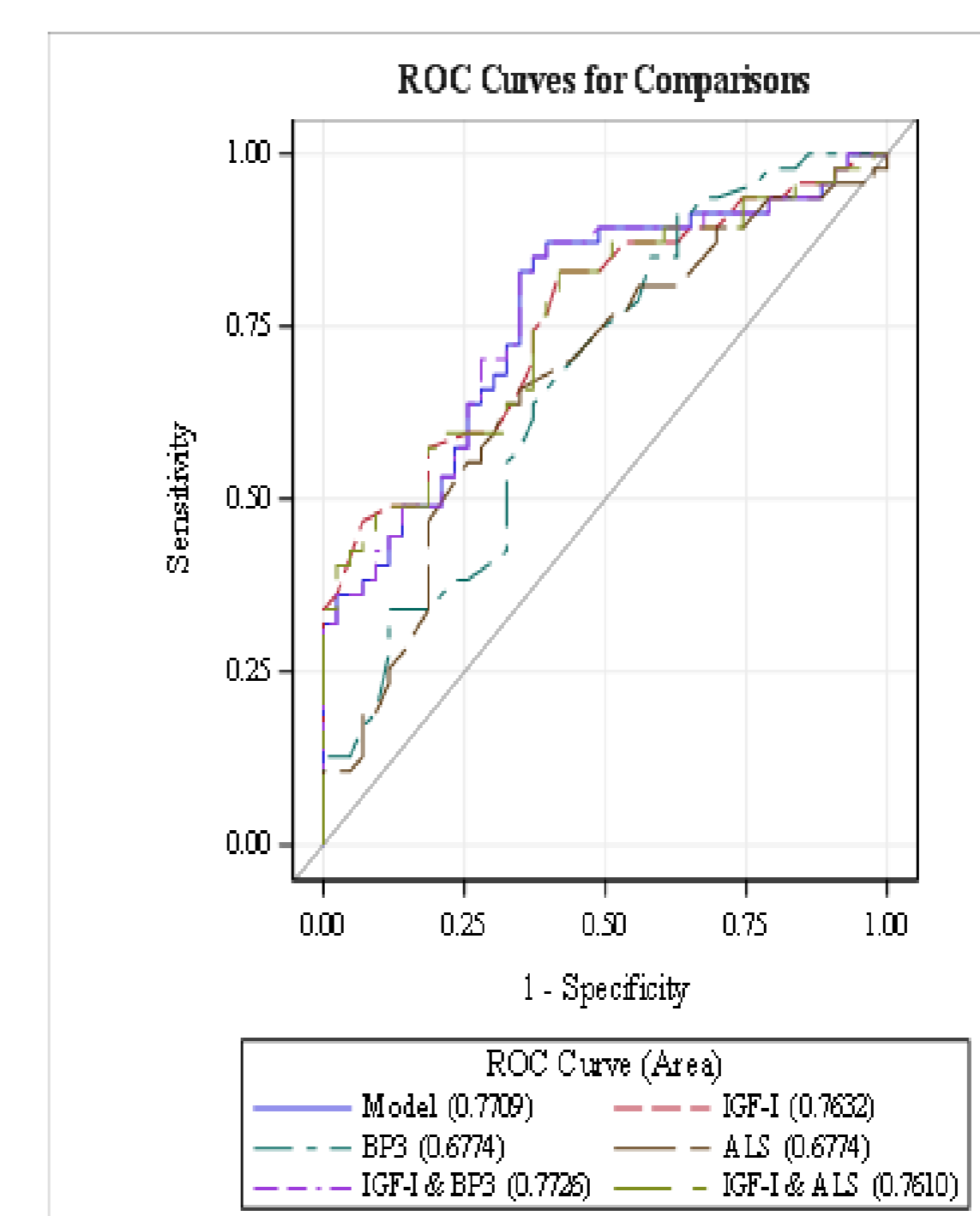
## Results:

48 participants presented with GH values less than 7 ng/ml, 43 individuals with values above it. Mean IGF-1, IGFBP-3 and ALS on the day of the test were lower in the participants with insufficient GH secretion. Apart from 4 participants, all other cohort members presented with ALS levels above -2 SDS on the day of the stimulation test.

**Table 1**

*Auxological and biochemical characteristics: median, mean, standard deviation, minimum and maximum for age (years), height (SDS), growth hormone peak (ng/ml), IGF-I, IGFBP-3 and ALS (SDS)*

Group		Age	Height	GH-peak	IGF-I	IGFBP-3	ALS
< 7 ng/ml	N	48					
	Median	8,5	-2,9	4,5	-1,8	-1,5	-1,1
	Mean ± SD	8,7 ± 3,9	-3 ± 1,0	4,1 ± 1,5	-1,8 ± 1,1	-1,6 ± 1,1	-1 ± 0,8
	Min./Max.	2,0/17,1	-5,6/-1,2	0,5/6,8	-4,6/1,1	-5/1	-2,4/1,7
≥ 7 ng/ml	N	43					
	Median	7,7	-2,9	8,4	-0,9	-0,7	-0,5
	Mean ± SD	8,7 ± 3,9	-3,1 ± 0,9	10 ± 3,7	-1 ± 0,9	-0,9 ± 1,0	-0,6 ± 0,7
	Min./Max.	3,3/16,9	-5,7/-1,0	7/23,0	-3,1/1,0	-3/1	-1,9/1,1



**Prediction of biochemical GH deficiency:** The area under the ROC curve (AUC) from a model containing only IGF-1 was 0.76, 0.68 respectively? when using only ALS. A model containing both, IGF-1 and IGFBP3, (AUC=0.77) was practically unchanged if ALS is added as a second or third parameter (AUC=0.76, AUC=0.77). Furthermore, the variation in the outcome (GH-peak < / >= 7) explained by IGF-1 only, amounts to 20.4% while that explained by IGFBP-3 and ALS is only 10.6% and 7.8%, respectively. For IGF-1, a -2 SDS cut-off delivers a sensitivity of 48% and a specificity of 83%. -1,5 SDS limit comes with a sensitivity and specificity. of 65%. For IGFBP-3, -2 SDS represents a sensitivity of 65%, by -1,5 SDS of only 53%. An ALS cut-off value of -2 SDS comes with sensitivity between 8-10%. Sensitivity values above 80% were seen starting with -0,4 SDS, a point where specificity is already under 50%.

## Conclusion:

Serum ALS measurement alone should not be used in the diagnostic work-up of short stature. Combining the measurement of ALS with IGF-I and IGFBP-3 does not improve the chances of diagnosing GHD.

## References:

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[2] Grote FK, van Dommelen P, Oostdijk W, de Muinck Keizer-Schrama SM, Verkerk PH, Wit JM, van Buuren S: Developing evidence based guidelines for referral for short stature. Arch Dis Child 2008; 93: 212–217.