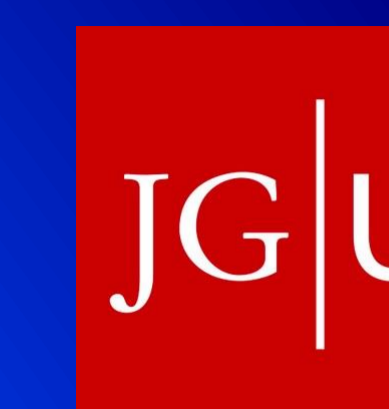


# THYROID STIMULATING AUTOANTIBODIES PREDICT ORBITOPATHY IN HASHIMOTO'S THYROIDITIS

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**Context:** Thyroid-associated orbitopathy (TAO) rarely occurs in patients with Hashimoto's thyroiditis (HT).

**Objective:** There is evidence that TSH receptor (TSHR) stimulating antibodies (TSAb) play a role in the pathogenesis of TAO. In this report, the prevalence of TSAb in HT patients with and without TAO was studied.

**Design:** Longitudinal observational study

**Setting:** Academic joint thyroid-eye clinic

**Subjects:** 1055 patients with HT and controls were include

**Methods:** TSAb was measured with a FDA-cleared bioassay that utilizes CHO cells expressing a chimeric TSHR and a cAMP response element-dependent luciferase. Results of TSAb activity were reported as percentage of specimen-to-reference ratio (SRR%, cut-off >140%).

**Main outcome measure:** Association of TSAb with the risk of TAO in patients with HT.

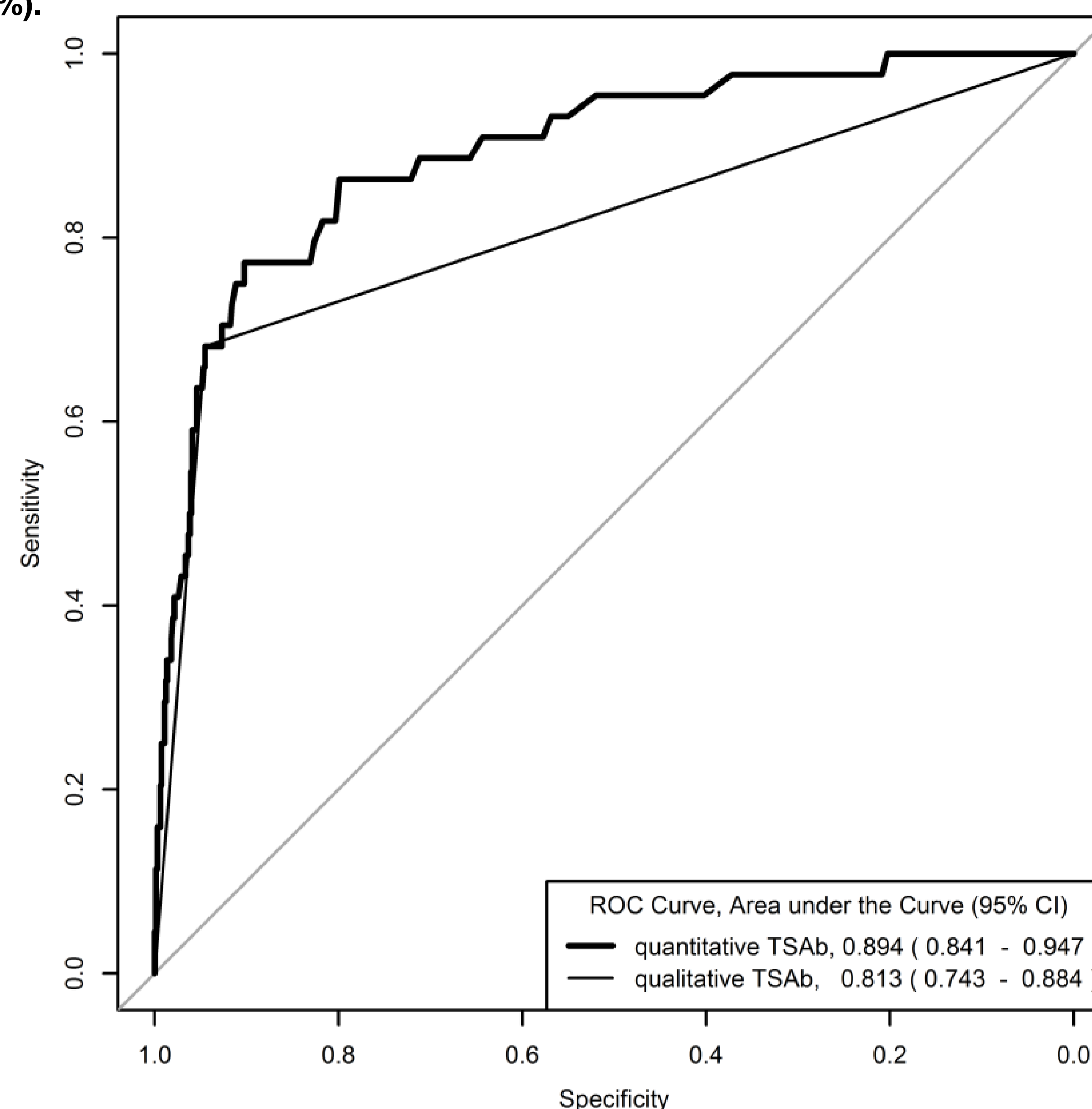
**Results:** Of 700 consecutive and unselected patients with HT, 44 (6%) had overt TAO. Patients with HT+TAO were older ( $p<0.001$ ), heavy smoker ( $p=0.032$ ), and clustered less with autoimmune diseases ( $p=0.005$ ). All healthy controls were TSAb negative. In contrast, serum was TSAb positive in 30/44 (68.2%) and 36/656 (5.5%,  $p<0.001$ ) patients with HT+TAO and HT, respectively. Compared to patients with HT only, serum TSAb levels were higher in HT+TAO (Median SRR%, 25% and 75% percentile): 45, 35-65 vs. 192.5, 115-455.3,  $p<0.001$ . Highest TSAb values were noted in patients with active and severe TAO versus those with mild and inactive TAO: 486, 392-592 versus 142, 73-192.5,  $p<0.001$ . The odds ratio (OR) of TSAb-positivity for the risk of TAO adjusted for gender and age was 55.9 (95% CI 24.6-127,  $p<0.0001$ ), while the OR per ten-fold change in TSAb SRR% (quantitative TSAb) was 133 (95% CI 45-390,  $p<0.0001$ ). The area under the ROC-curve for qualitative and quantitative TSAb was 87.2% (95% CI 80.6-93.8) and 89.4% (95% CI 84.1-94.7), respectively.

**Conclusions:** TSAb is strongly associated with TAO in HT and TSAb may contribute to the pathophysiology of TAO.

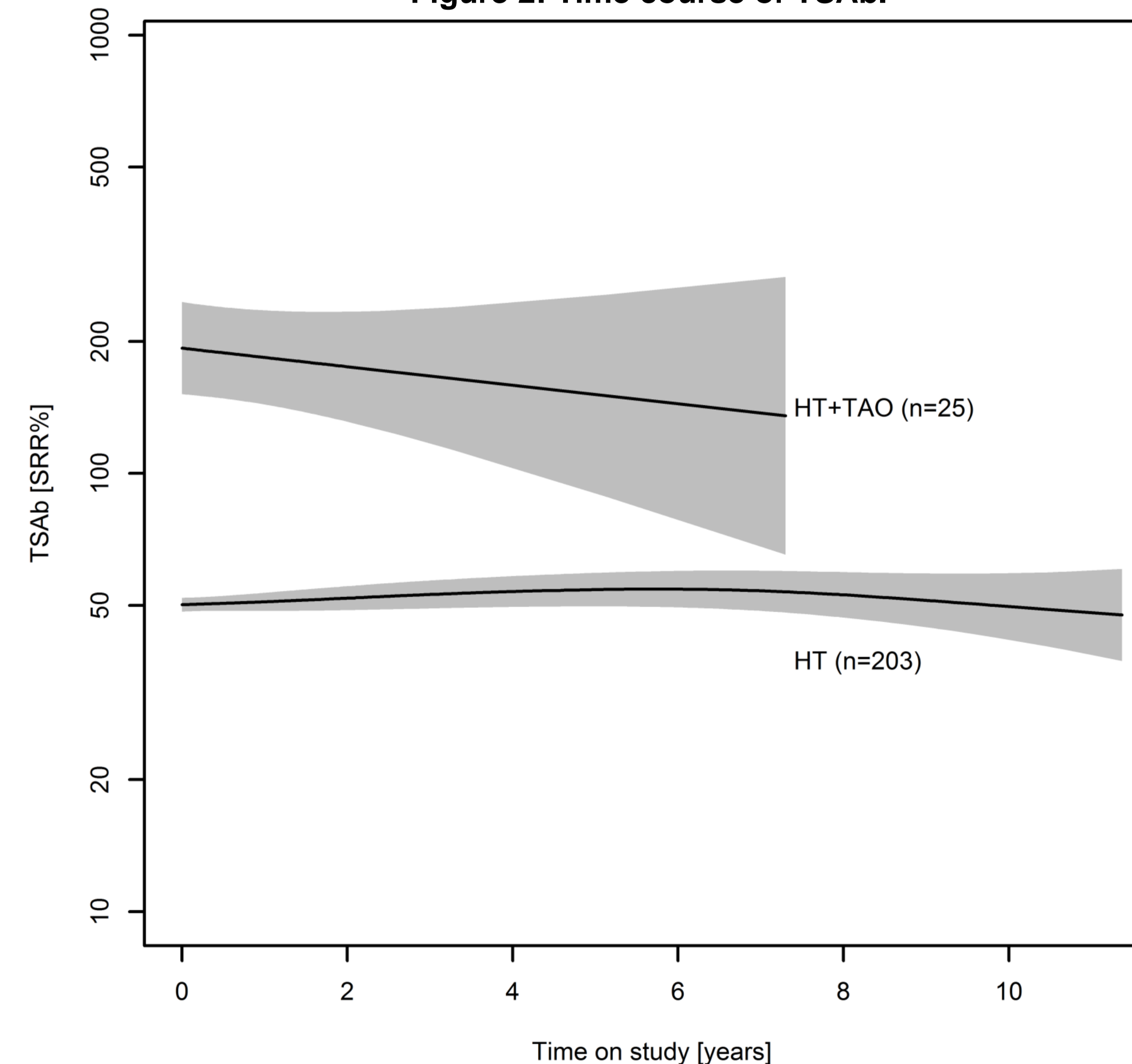
**Table 1: Demographic Data of 700 consecutive patients with Hashimoto's thyroiditis without (HT) or with associated orbitopathy (HT + TAO)**

	HT	HT + TAO	P-value
<b>N (%)</b>	656 (94)	44 (6)	
<b>Age (years)</b>	35.2 (17.3-48.3)	49.3 (31.8-56.1)	<0.001
<b>Duration of HT (years)</b>	0.9 (0-5.6)	2.4 (0.1-9)	0.028
<b>Female</b>	543 (83)	37 (84)	0.823
<b>Children (&lt; 18 years)</b>	171 (26.1)	4 (9.1)	0.012
<b>Heavy smoker (20 cig/day/year)</b>	84 (16.6)	12 (30)	0.032
<b>L-T4 therapy, N (%)</b>	376 (58.4)	28 (65.1)	0.385
<b>Monoglandular disease</b>	345 (52.6)	33 (75)	0.004
<b>Polyglandular disease</b>	147 (22.4)	2 (4.5)	0.005
<b>HT + type 1 diabetes</b>	107 (16.3)	1 (2.3)	0.013
<b>HT + Addison's disease</b>	23 (3.5)	1 (3.5)	0.663
<b>HT + autoimmune gastritis</b>	68 (10.4)	3 (6.8)	0.450
<b>HT + pernicious anemia</b>	25 (3.8)	2 (4.5)	0.802
<b>HT + celiac disease</b>	36 (5.5)	0	0.111

**Figure 1: Receiver operating characteristic (ROC) curve for discriminating between patients with and without TAO by quantitative and qualitative TSAb measurements (using the cut-off 140 SRR%).**



**Figure 2: Time course of TSAb.**



Predicted values and 95% confidence bands based on fitting an additive model for correlated data to longitudinal TSAb measurements from 25 patients with and 203 patients without TAO with more than one measurement. For patients with TAO, measurements did not start before the year of reported onset of TAO. The model describes the average outcome, which is allowed to depend smoothly on time of study.

**Table 2: Serological Data of 700 consecutive patients with Hashimoto's thyroiditis without (HT) or with associated orbitopathy (HT + TAO) and of 53 control patients with Graves' disease without (GD) or with associated orbitopathy (GD+TAO)**

	HT	HT + TAO	P-value	GD	GD + TAO	P-value
<b>N (%)</b>	656 (94)	44 (6)		26	27	
<b>TSAb positive patients, N (%)</b>	36 (5.5)	30 (68.2)	<0.001	26 (100)	27 (100)	
<b>TSAb positive samples, N (%)</b>	67 / 1128 (8)	103 / 141 (73)	<0.001	437 (306-520)	654 (588-864)	<0.001
<b>TSAb SRR% (patients)</b>	45 (35-65)	193 (115-455)	<0.001			
<b>TSAb SRR% (samples)</b>	46 (35-63)	304 (122-518)	<0.001			
<b>TSAb SRR% in smokers</b>	43 (34-61)	176 (85-291)	<0.001	436 (268-694)	645 (583-739)	0.019
<b>TSAb SRR% (hypothyroid pts.)</b>	47 (35-67)	189 (104-476)	<0.001			
<b>TBII positive, N (%)</b>	35 (5)	22 (51)	<0.001	26 (100)	27 (100)	
<b>TBII (&lt; 1.8 IU/L)</b>	0.5 (0.5-0.5)	1.8 (0.5-6.5)	<0.001	6.3 (3.6-16)	12 (6-32)	0.027
<b>TSH (0.4-4.9 mU/L)</b>	1.8 (0.8-3.8)	0.9 (0.4-2.4)	0.002	0.01 (0.01-0.01)	0.01 (0.01-0.01)	0.146
<b>FT3 (1.7-3.7 pg/ml)</b>	3 (2.6-3.4)	2.9 (2.5-3.2)	0.362	6.75 (5.1-11.1)	11 (5.4-14.2)	0.182
<b>FT4 (0.7-1.5 ng/dl)</b>	1.2 (1-1.4)	1.1 (1-1.3)	0.186	1.95 (1.7-2.4)	2.2 (1.9-2.7)	0.218
<b>Tg (&lt; 55 ng/ml)</b>	3.3 (0.3-14.3)	2.9 (0.6-12.3)	0.755	95 (41-224)	249 (97-815)	0.043
<b>Tg-Ab (&lt; 4.1 IU/ml)</b>	59 (9.3-303)	74 (8.2-386)	0.525	5.1 (2.4-40)	5.4 (1.4-1000)	0.593
<b>TPO-Ab (&lt; 6 IU/ml)</b>	182 (38-526)	158 (73-903)	0.917	301 (37-956)	299 (4-786)	0.693

**Table 3: Clinical and serological data in 44 patients with Hashimoto's associated orbitopathy (HT+TAO) according to the clinical activity and severity of TAO**

	Mild / inactive	Severe / active	P-value
<b>Patients, n=44 (%)</b>	29 (66)	15 (34)	
<b>Samples, n=141</b>	72	69	
<b>Age (years)</b>	46 (31-55)	51 (44-57)	0.185
<b>Female</b>	25 (86.2)	12 (80)	0.594
<b>Smoker</b>	9 (35)	3 (20)	0.385
<b>Hypothyroid</b>	20 (69)	10 (67)	0.877
<b>Euthyroid</b>	7 (24)	3 (20)	0.756
<b>Hyperthyroid</b>	2 (7)	2 (13)	0.481
<b>TSAb positivity (patients)</b>	13 (44.8)	15 (100)	<0.001
<b>TSAb positivity (samples)</b>	35 (48.6)	68 (99)	<0.001
<b>TSAb SRR% levels (patients)</b>	142 (73-193)	486 (392-592)	<0.001
<b>TSAb SRR% levels (samples)</b>	133 (68-195)	512 (452-574)	<0.001
<b>TBII positivity (patients)</b>	10 (34)	12 (80)	0.006
<b>TBII levels (&lt; 1.8 IU/L)</b>	0.7 (0.5-3.4)	6.3 (2.1-16)	0.001

**Table 4: Association of the first TSAb measurement with TAO assessed by means of logistic regression.**

Predictor	Adjustments	Odds Ratio (95% CI)	P-value
<b>TSAb positive (SRR &gt; 140%)</b>	None	36.9 (18.0-75.7)	<0.0001
	Age, sex	55.9 (24.6-127)	<0.0001
<b>TSAb (per 10-fold change)</b>	None	102 (38-273)	<0.0001
	Age, sex	133 (45-390)	<0.0001