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Article

# Ultrasound and Clinical Parameters in Patients with Hashimoto's Thyroiditis Related to Dermatological Diseases: A Cross-Sectional Study

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**Abstract:** Background: Hashimoto's thyroiditis (HT) is an autoimmune disease that progressively leads to thyroid gland destruction and hypothyroidism. Patients produce antibodies against two thyroid-specific antigens: thyroglobulin and thyroid peroxidase. As a result of the abnormal amount of thyroid hormone produced and its autoimmune etiology, patients with HT display a higher frequency of either autoimmune or non-autoimmune dermatological disorders. On ultrasound examination, HT can be detected by observing an enlarged thyroid gland with hypochoic parenchymal regions or by observing a small gland indicating atrophy and diffusely heterogeneous parenchyma. Changes in the parenchymal vascularity can be observed as decreased or increased levels of vascularization. Objective: This study aimed to analyze the role of clinical data and ultrasound evaluation of patients with HT in suggesting an association with dermatological disorders. Patients and methods: Complete dermatological and endocrinological assessments as well as ultrasonography of the thyroid and lymphnodes were performed in HT patients. Results: The data obtained showed that a family history of thyroid disease, increased diameter of the inferior thyroid artery, and the presence of cervical lymphadenopathy were more frequent in the group of patients with dermatological diseases. Taken together, our results suggest the usefulness of ultrasound in determining a possible association between HT and dermatological disorders.

**Keywords:** Hashimoto's thyroiditis; dermatological disorders; familiarity; thyroid vascularization; lymphadenopathy; ultrasonographic parameters

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## Introduction

Autoimmunity occurs when a reduction in regulatory T lymphocytes causes a breakdown of immune tolerance toward self-antigens.[1–3] Hashimoto's thyroiditis (HT) is an autoimmune thyroid disorder characterized by the presence of anti-thyroglobulin (Ab-TG) and/or anti-thyroid peroxidase (Ab-TPO) autoantibodies that cause a cellular and humoral immune response that destroys the thyroid gland. The resulting tissue fibrosis and gland atrophy lead to hypothyroidism in 20–30% of patients and are the most common causes of hypothyroidism in developed countries.[4,5] An early *post-mortem* study that analyzed patients with no evidence of thyroid disease during their lifetime revealed that 27% of adult women and 7% of men had thyroiditis, suggesting that the prevalence of

autoimmune thyroiditis is probably underestimated.[6,7] The reported incidence of HT is higher in women, in iodine-deficient areas, and in older patients.[5,8] Detecting the presence of autoantibodies in peripheral blood enables the HT diagnosis; however, diagnosis can be challenging, and delays are not uncommon.[8] Ab-TPO antibody titer can also predict the development of overt thyroid dysfunction (in which thyroid-stimulating hormone (TSH) and thyroid hormone abnormalities are present). In contrast, the Ab-TG sensitivity is lower (30–50%).[5] On ultrasound examination, HT may initially present as an enlarged thyroid gland with multiple small hypoechoic nodules surrounded by areas of healthy, fibrosis thyroid parenchyma in a pattern resembling that of giraffe skin.[9] The gland appearance progresses to chronic hypertrophic thyroiditis, which is diffusely enlarged and characterized by multiple hypoechoic pseudo nodules separated by fibrotic bands. In some cases, the gland may further progress to the atrophic form, thus becoming smaller, with ill-defined contours and diffusely heterogeneous parenchyma. In the latter chronic phase of HT, ultrasound findings include a small, ill-defined gland with diffusely heterogeneous parenchyma and absence of flow on Doppler ultrasound due to extensive fibrosis.[10] The parenchymal vascularity can vary from hypovascular to diffusely hypervascular.[11] Hypervascularity results from the action of elevated levels of TSH and decreases when TSH levels normalize.[12,13] In HT, hypervascularity is usually mild, and blood flow rates are within normal limits.[14] The resistive index (RI) value in patients with thyroiditis is significantly lower than that in healthy subjects, regardless of the degree of vascularization. This value, especially in pediatric patients, assumes a key role in the ultrasound diagnosis of thyroiditis and appears to correlate positively with the degree of glandular fibrosis.[15] Patients with HT frequently display reactive cervical lymph node enlargement, which seems related to the autoimmune process.[16]

The association between HT and dermatological disorders has been widely demonstrated. Skin manifestations associated with HT fall into two categories: i) diseases caused by the action of thyroid hormones on the skin and ii) immune-mediated inflammatory skin diseases (IMID) that have a known or suspected autoimmune etiology.[17–19] This second type of skin disease is significantly more frequent in patients with HT because of the genetic predisposition to develop autoimmunity.[20] Indeed, it has been found to be associated with vitiligo, alopecia areata, systemic lupus erythematosus, systemic sclerosis, bullous pemphigoid, and vulgar pemphigus.[21–27]

This study aims to evaluate clinical and ultrasound parameters in patients with HT and their possible association with the concomitant presence of dermatological pathologies.

## **Patients and Methods**

### *Study Design*

This is a cross-sectional observational study in which 100 patients with HT, defined by the presence of positive Ab-TPO (regardless of the time of the diagnosis), aged  $\geq 18$  years, were enrolled. These patients attended the endocrinology outpatient clinic and signed a regular informed consent.

### *Endocrinological Examination*

According to clinical practice, enrolled patients underwent endocrinological examination with evaluation of thyroid function, including TSH, free thyroxine (FT4), free triiodothyronine (FT3), and autoantibodies against the two thyroid-specific antigens: Ab-TG and Ab-TPO.

### *Ultrasound Evaluation*

All ultrasound examinations were performed with an Esaote MyLab Eight XP ultrasound machine by two sonographers with more than 10 years of experience.

Ultrasound parameters that contribute to the diagnosis of thyroiditis consist of the B-mode assessment (glandular volume, echotexture and echogenicity of thyroid parenchyma, presence of nodulations), the color Doppler vascularity with calculation of the RI of the inferior thyroid artery (ITA) and the presence and location of reactive lymph nodes were also evaluated. The analysis of the echogenicity of the thyroid parenchyma was performed subjectively by comparing it with the

echogenicity of the prethyroid muscles and submandibular gland, classifying it as isoechogenic, hyperechogenic, and hypoechogenic with respect to these structures. The normal thyroid gland typically exhibits greater echogenicity than the prethyroid muscles and is slightly higher than the submandibular glands. Thyroid parenchyma is considered hypoechoic when its echo levels are similar or lower than those of the submandibular glands but higher than those of the muscles (slightly hypoechoic) or are similar to those of the prethyroid muscles (hypoechoic). On sonography examinations, cervical lymph nodes are usually classified into eight regions. Normal and reactive lymph nodes are usually found in submandibular, parotid, superior cervical, and posterior triangle regions. On gray-scale ultrasonography, normal and reactive lymph nodes tend to be hypoechoic with respect to adjacent muscles and oval (short to long axis ratio (S/L) <0.5), except for submandibular and parotid lymph nodes, which are usually round (S/L  $\geq$ 0.5) and have an echogenic hilum. On color Doppler, power Doppler, and 3D sonography, normal cervical lymph nodes show hilar vascularity or appear avascular, whereas reactive lymph nodes show predominantly hilar vascularity. Inflammation causes vasodilatation, which increases blood flow velocity in reactive lymph nodes.

#### *Dermatological Examination*

All enrolled patients were examined by a dermatologist who collected a detailed medical history (personal or family medical history, occupational exposures, long-term exposure to sunlight or other forms of radiation, drug use, etc.) and performed an examination of the entire skin surface, as well as hair, nails and mucous membranes to assess dermatological diseases. The dermatological examination was performed using an appropriate light source and magnification, assessing the skin lesions' distribution, location, size, demarcation, morphology, and color. Dermoscopy and Wood's lamp were used, microscopic and culture examinations for germ and fungal were carried out, and skin biopsy was used as an additional diagnostic tool when needed.

#### *Statistical Analysis*

Categorical variables were reported through absolute and relative frequencies, while continuous variables were reported through median values and min–max intervals. The Kolmogorov-Smirnov normality test was calculated for all the continuous variables. The Mann–Whitney U test or Student's t-test was performed to explore the differences between continuous variables, depending on the nature of the data distribution. The relationships between categorical variables were analyzed using Pearson's chi-squared test or Fisher's exact test, as appropriate. The correlations between variables were evaluated using Spearman's Rank correlation coefficient.  $p \leq 0.05$  was considered statistically significant. Statistical analyses were carried out using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA).

### **Results**

One hundred patients were enrolled in this cross-sectional study, 92% female and 8% male, with a median age of  $43.66 \pm 12.40$  years. Dermatological diseases were detected in 53% of patients, including 42% with immune-related pathologies and 11% with non-immune-related dermatological diseases, as summarized in Figure 1 and Supplementary Table S1. To assess the factors that increased the risk of dermatological manifestations, patients were categorized into two groups: patients without concomitant dermatological diseases (group 1, 58 patients) and those with dermatological diseases (group 2, 42 patients). Data about age, sex, body mass index, and familiarity for thyroid disorders (Table 1), as well as TSH, FT3, FT4, Ab-TPO, Ab-TG (Table 2) and thyroid ultrasound parameters levels (Table 3) were collected. The two groups were homogeneous for sex and age, while there was a statistically significant difference in the percentage of family history of thyroid disorders (22.4% in group 1 vs 52.4% in group 2,  $p=0.002$ , Table 1). In most cases, patients had normal thyroid function; thyroid function was not different between groups (Table 2). Based on the diagnosis of HT, the mean antibody titer was significantly altered in all patients (Ab-TPO: 155.5 (9–11,728) UI/ml in group 1; Ab-TPO: 193 (10–13,000) UI/ml in group 2; Ab-TG: 152.5 (9–3,854) UI/ml in group 1; Ab-TG:

97.0 (4.6–1,000) UI/ml in group 2 (Table 2)). At ultrasound examination, the most prevalent thyroid features were enlargement and hypervascularization of the gland accompanied by lymphadenopathy (Figure 2). Our study found that within patients with thyroiditis and increased ITA diameter was observed in the case of concomitant dermatological pathologies. Indeed, there was a statistically significant difference in either the left ITA diameter, 1.2 (0.8–16) mm in group 1 and 1.6 (0.8–16) mm in group 2 ( $p=0.023$ ), or in the right ITA diameter, 1.2 (0.7–3) mm in group 1 and 1.5 (0.9–2.9) mm in group 2 ( $p=0.005$ , Table 3). No statistical difference in RI was found between the two groups, with a mean RI of 0.6 in group 1 and 0.7 in group 2. In addition, 86.3% of patients in group 1 and 100.0% in group 2 showed the presence of reactive lymph nodes, with a statistically significant difference between groups ( $p=0.016$ , Table 3).

**Table 1.** Demographic characteristics of patients with Hashimoto's thyroiditis and correlations with dermatological disorders.

	Dermatological disease		p-value
	No (n=58)	Yes (n=42)	
Age (years), median (min–max)	48 (19–72)	44.5 (22–72)	0.869 <sup>†</sup>
BMI, median (min–max)	23.7 (17.3–43.9)	22.2 (17.6–35.7)	0.262 <sup>‡</sup>
Sex, n (%):			
• Female	53 (91.4)	39 (92.9)	0.999 <sup>§</sup>
• Male	5 (8.6)	3 (7.1)	
Familiarity, n (%):			
• No	45 (77.6)	20 (47.6)	0.002 <sup>¶</sup>
• Yes	13 (22.4)	22 (52.4)	

<sup>†</sup>Student's t-test; <sup>‡</sup>Mann–Whitney test; <sup>§</sup>Fisher's exact test; <sup>¶</sup>Pearson's chi-squared test.

**Table 2.** Study of the correlation between dermatological disorders and thyroid hormone and autoantibody levels.

	Dermatological disease		Mann–Whitney test (p-value)
	No (n=58), median (min–max)	Yes (n=42), median (min–max)	
TSH:	2.9 (0.1–22.2)	2.8 (0.1–12.5)	0.632
• ≤4.5	42 (72.4)	33 (78.6)	0.483 <sup>†</sup>
• >4.5	16 (27.6)	9 (21.4)	
FT3	3 (0.9–12.7)	3.1 (0.8–20.0)	0.955
FT4	1.2 (0.2–26.0)	1.1 (0.6–12.0)	0.834
Ab-TPO	155.5 (9.0–11,728.0)	193.5 (0.7–13,000.0)	0.617
Ab-TG	152.5 (0.3–3,854.0)	97.0 (4.6–1,000.0)	0.078

<sup>†</sup>Fisher's exact test.

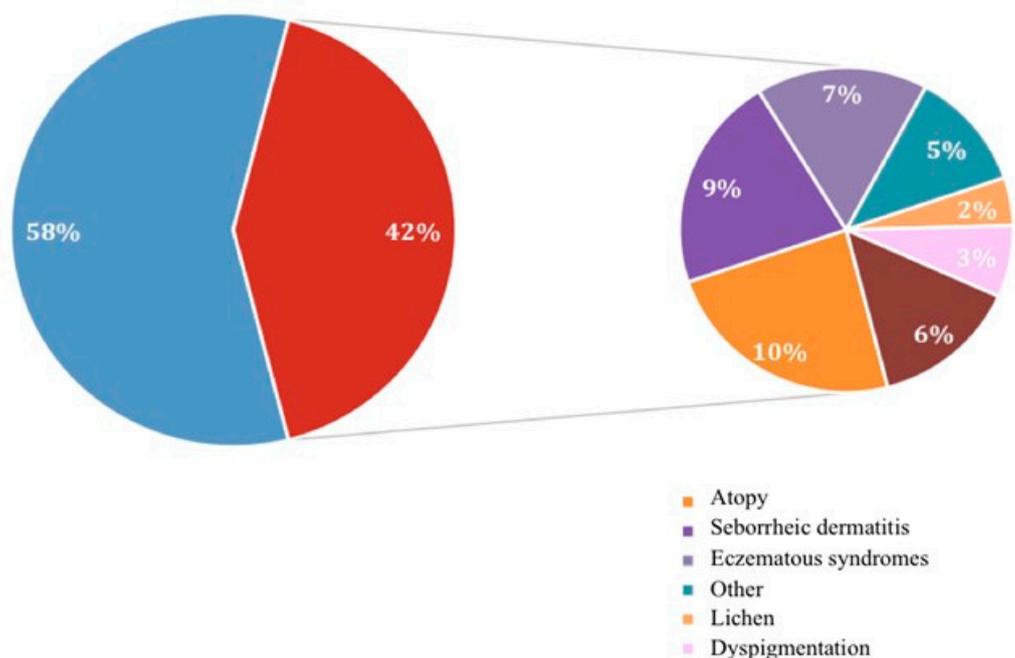
**Table 3.** Correlation of thyroid ultrasound parameters with dermatological disorders.

	Dermatological disease, median (min–max)/n (%)		Mann–Whitney test (p-value)
	No (n=58)	Yes (n=42)	
AP thyroid size (mm):			
• Right lobe	14.5 (1.54–26.0)	15 (8.0–35.0)	0.517
• Left lobe	15.0 (1.7–26.0)	15.4 (9.0–49.0)	0.230
Thyroid nodule size (mm)	7.0 (2.0–27.0)	7.0 (0.7–20.0)	0.525
Regular margins:			
• No	27 (46.6)	12 (29.3)	0.083 <sup>†</sup>

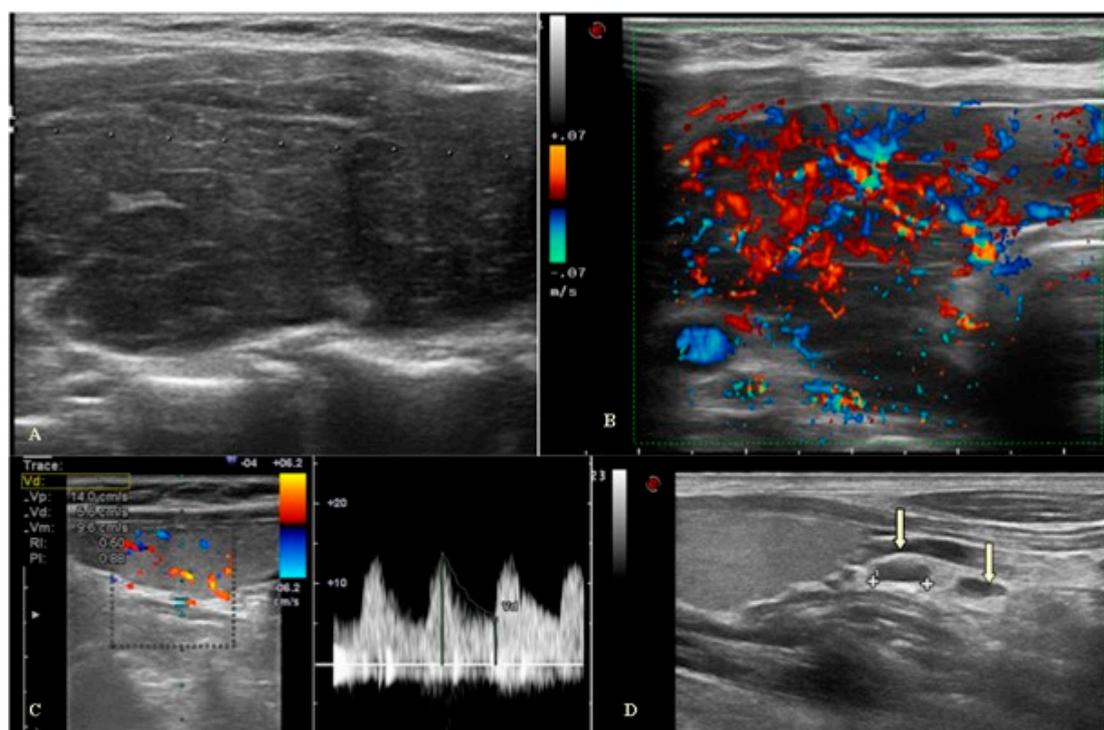
• Yes	31 (53.4)	29 (70.7)	
Thyroid echogenicity:			
• Hypoechogenicity	50 (86.2)	37 (90.2)	0.648 <sup>†</sup>
• Hyperechogenicity	7 (12.1)	4 (9.8)	
• Normoechogenicity	1 (1.7)	0 (0.0)	
Parenchymal vascularity:			
• Normal-decreased parenchymal vascularity	13 (22.4)	13 (31.7)	0.301 <sup>†</sup>
• Increased parenchymal vascularity	45 (77.6)	28 (68.3)	
Lymph node level:			
• Cervical	7 (12.3)	0 (0.0)	0.039 <sup>‡</sup>
• Pretracheal	50 (87.7)	41 (100.0)	
Inferior thyroid RI and diameter:			
• Left ITA RI	0.6 (0.5–0.9)	0.7 (0.5–0.8)	0.237
• Right ITA RI	0.6 (0.5–0.8)	0.7 (0.5–0.7)	0.116
• Left ITA diameter (mm)	1.3 (0.8–16.0)	1.6 (0.8–16.0)	0.023
• Right ITA diameter (mm)	1.2 (0.7–3.0)	1.5 (0.9–2.9)	0.005

<sup>†</sup>Pearson's chi-squared test; <sup>‡</sup>Fisher's exact test. ITA: inferior thyroid artery; RI: resistive index.

### Dermatological evaluation



**Figure 1.** Prevalence of dermatological diseases in our population.



**Figure 2. Thyroiditis ultrasonographic aspects.** Enlarged thyroid gland, with hypoechoic aspect (A) and with diffuse hypervascularization (B). Reduction in the value of the inferior thyroid artery resistive index (C). Parathyroid lymph nodes enlargement (D).

## Discussion and Conclusions

HT is characterized by strong genetic susceptibility and polymorphism of several genes associated with disease occurrence and severity. Its autoimmune etiology and altered thyroid hormone levels implicate the association between HT and IMID.[26,28] IMID comprise atopic dermatitis, acne, vitiligo, psoriasis, and alopecia areata, which share the features of chronic inflammation[29–31] and are characterized by a complex multifactorial etiology in which genetic and environmental factors contribute to disease development.[17,32]

Our study showed a high prevalence of both autoimmune and non-autoimmune dermatological disorders in our cohort of patients with HT. Accordingly, the association between HT and several dermatological disorders was demonstrated. Indeed, the association between HT and vitiligo is strongly supported by available data from large cohort studies.[33–37] Additionally, multiple explanations for the molecular mechanisms of this association have been proposed, such as the presence of shared hereditary susceptibility genes or the expression of melanocyte-specific antigens in the thyroid gland.[33,37] In a meta-analysis, the authors found a statistically significant increased incidence of thyroiditis in the group of patients with melasma compared with controls.[38] In addition, a retrospective study on 9,654 patients with psoriasis demonstrated a significant association between this dermatological disorder and HT.[29,39] HT is also associated with urticaria,[40–42] lupus erythematosus,[26,37,43] alopecia areata,[44,45] lichen[19,46–48] and scleroderma.[23] Specifically, in patients with scleroderma presenting with complications in pregnancy, authors found that 53% had thyrotoxicosis due to HT.[49] However, less is known about the prevalence of non-autoimmune dermatological disorders in patients with thyroiditis. Prevalence differs significantly among studies, probably because of the different ranges of antibody titers used as a normal reference and the possibility that antibody titers may change during the natural history of the disease.[50]

Furthermore, while no association was found between thyroid hormone levels and the presence of dermatological diseases in our cohort, a more frequent family history of thyroid disease was observed in the group of patients with dermatological problems. Accordingly, for both thyroiditis and dermatitis, familiarity has been extensively demonstrated and linked to the human leukocyte

antigens (HLA) locus.[17,32,51] Regarding family history in HT, linkage and association studies have identified several genes involved in the occurrence of autoimmune thyroid disease (AITD), including the thyroglobulin gene and genes shared with other autoimmune diseases involved in regulating immunity. Genetic screenings have identified the *HLA* locus, in particular *HLA-DR3*, as a predisposing factor for HT.[52] Another important AITD immune response susceptibility gene is *CD40*, which plays a key role in the cross-talk between antigen-presenting cells and T cells.[51] Studies involving families, populations, and epidemiological research have shown that genetic risk patterns of skin diseases such as psoriasis are linked to HLA locus.[53]

Finally, clinical and radiological characteristics were evaluated to determine whether they could predict the presence of dermatological diseases, considering both those with and those without an autoimmune etiology in our cohort of patients. Interestingly, our study showed that a significantly higher thyroid vascularization and cervical lymphadenopathy characterized our cohort of patients with HT displaying dermatological disorders. In the literature, there is no reference level characterizing thyroid vascularization in HT, as this pathology presents with varying degrees of vascularity.[54] Indeed, increased glandular vascularization does not seem related to thyroid function and appears purely expressive of inflammatory activity.[55] Thus, the increased thyroid vascularization observed in patients with HT presenting with dermatological disorders could reflect the hyper-inflammatory state of this population. On the other hand, lymph node assessment is critical in diagnosing patients with thyroid pathology, especially considering the frequency of coexisting benign and malignant diseases and the propensity of malignant thyroid disease to metastasize to regional lymph nodes. Paratracheal lymph node hyperplasia was found more often in patients with HT than in controls.[16] In another study, enlarged cervical lymph nodes were detected during neck ultrasound examination in 62.5% (n=25) of patients with HT.[56] However, the presence of lymph nodes in intrathyroidal and pretracheal sites indicated HT with a specificity of 97.8%. Hyperplasia of regional lymph nodes is associated with clonal expansion of autoreactive T and B cells. It represents an early stage of the disease, while later lymphoid tissue frequently develops in the thyroid itself.[57] However, to our knowledge, there is no study in the literature associating cervical lymphadenopathy in patients with HT and the presence of dermatological disorders.

The study's main limitation lies in the number of patients included, which impedes the drawing of more robust conclusions. However, the study evidenced a higher frequency of dermatological disease in patients with HT, particularly in the case of a family history of thyroid disease and in the presence of vascular flow alteration and cervical lymphadenopathy. Furthermore, based on the results obtained, it is possible to speculate on the usefulness of ultrasound evaluation of cervical lymph nodes and ITA in determining the risk of developing dermatological disorders. Early recognition and treatment of dermatological diseases would promote a better quality of life for patients.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

**Authors' contributions:** F.D. was responsible for the conception and design of the study. F.D., A.G., F.E. and F.M.S. were responsible for ultrasound evaluation. A.B., G.P. and M.M. were responsible for follow-up of patients and F.S. was responsible for statistical analysis. All the authors were responsible for data interpretation, writing, revision, and final approval of the manuscript.

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**Ethics:** This study was approved by the Central Ethical Committee IRCCS Lazio Sezione IFO - Fondazione G.B. Bietti on 22/11/2016 under the number 878/16 RX ISG. The study was conducted in accordance with Good Clinical Practice (GCP), ICH topic E6 (R2 and CFDA GCP) guidelines, the rules of the Declaration of Helsinki, all applicable local law requirements and regulations concerning the privacy and security of personal information, including the General Data Protection Regulation (GDPR) (EU) 2016/679. Informed consent was obtained from all patients participating in the study.

**Data availability statement:** All data generated and analyzed during this study are available within the paper. Further inquiries can be directed to the corresponding author.

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**Conflicts of interest:** The authors declare that they have no conflicts of interest.

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