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Prognostic value of acoustic structure quantification in patients with Hashimoto's thyroiditis

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Abstract

Objectives Assessment of thyroid parenchymal echogenicity on ultrasonography is a predictor of future thyroid dysfunction. Our objective was to determine the prognostic value of acoustic structure quantification (ASQ) to predict the outcome of patients with Hashimoto's thyroiditis (HT).

Materials and methods We prospectively evaluated 90 patients with HT using ASQ from May to December 2013. Surveillance for the development of overt hypothyroidism was conducted over a median period of 40 months (3–55). ASQ were dichotomized based on optimal cutoff values obtained from ROC curve analysis. The probability of developing overt hypothyroidism was compared between the dichotomized subgroups using Kaplan–Meier analysis and log-rank tests. Multivariate Cox regression analysis was performed to determine significant prognostic factors.

Results The cumulative rate of overt hypothyroidism was 67.7%. The median interval to overt hypothyroidism was 27.9 months (95% confidence interval, 12.0–38.0 months). There was no significant difference in the risk of overt hypothyroidism using qualitative echogenicity between groups ($p = 0.669$) according to Kaplan–Meier analysis. However, the ASQ average ($p < 0.001$), standard deviation ($p = 0.015$), and focal disturbance ratio ($p < 0.001$) were significantly associated with an increased risk of overt hypothyroidism. Multivariate Cox regression analysis revealed that a higher ASQ average (hazard ratio, 1.03; $p = 0.03$) and higher thyroid-stimulating hormone level (hazard ratio, 1.02; $p = 0.02$) were independent predictors of overt hypothyroidism.

Conclusions ASQ has potential as a prognostic biomarker for predicting the risk of overt hypothyroidism in patients with HT.

Key Points

- *ASQ provides quantitative prognostic information of thyroid parenchymal echogenicity.*
- *ASQ parameters improved the stratification of patients who are prone to develop overt hypothyroidism in HT.*
- *ASQ can serve as prognostic biomarker in HT.*

Keywords Thyroiditis, lymphocytic · Autoimmune thyroiditis · Thyroiditis · Hypothyroidism · Ultrasonography

Abbreviations

ASQ	Acoustic structure quantification
FD	Focal disturbance
HT	Hashimoto's thyroiditis
SD	Standard deviation
Tg	Thyroglobulin
TPO	Thyroperoxidase
TSH	Thyroid-stimulating hormone
US	Ultrasound

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Introduction

Hashimoto's thyroiditis (HT) is the most common cause of hypothyroidism in iodine-sufficient countries. The onset of HT is insidious, and the condition may not be clinically apparent until development of the full range of symptoms [1]. As a result, subclinical hypothyroidism may go undetected for 10 years or even more. Subclinical hypothyroidism is defined as an elevated serum thyroid-stimulating hormone (TSH) level associated with normal free T4 and T3 values. Subclinical hypothyroidism is considered compensated hypothyroidism. The circulating levels of thyroid hormones are within the normal range, with only serum TSH being elevated; therefore, the affected subject is euthyroid because the increased TSH causes the thyroid gland to produce normal thyroid hormone levels. Persistent subclinical hypothyroidism has been associated with an increased risk of cardiovascular disease [2, 3], depression and cognitive dysfunction [4], various biochemical abnormalities such as elevated low-density lipoprotein cholesterol [5], and increased serum prolactin concentrations [6]. A major concern in these patients is the development of overt hypothyroidism over time. Overt hypothyroidism is defined as an elevated TSH with low T4 levels. Due to the high prevalence of this disease, early and accurate prediction of overt hypothyroidism is important.

Previous studies indicated that increased serum TSH and autoantibody levels are important predictors of overt hypothyroidism in patients with subclinical or euthyroid thyroiditis [7–11]. In addition to biochemical markers, the presence of abnormal parenchymal hypoechogenicity (findings of chronic thyroiditis) on gray-scale ultrasonography (US) is a well-known predictor, which can help to identify patients that are prone to develop overt hypothyroidism [12–16]. However, US has low-level inter-reader agreement when assessing subtle changes in parenchymal echogenicity [17]. Some efforts have been made to obtain quantitative information for lesion characterization using US, such as the use of various elastography techniques [18] and texture analysis [19].

Acoustic structure quantification (ASQ) is a commercially available software used to provide qualitative and quantitative information on acquired echo signals. Recent reports have shown that ASQ was clinically useful and reliable in diffuse liver disease [20] and thyroiditis [21–23]. However, to the best of our knowledge, the utility of ASQ for predicting future overt hypothyroidism has not been assessed in clinical studies.

Therefore, the purpose of this prospective study was to evaluate whether ASQ imaging can improve prediction of overt hypothyroidism in HT patients.

Materials and methods

Study population

The Institutional Review Board of Soonchunhyang University Bucheon Hospital approved this prospective study, and informed consent was obtained from all participants. The study eligibility criteria were (a) patients with a diagnosis of HT with a euthyroid or subclinical hypothyroid status (persistently elevated thyroid-stimulating hormone [TSH] in the presence of normal serum thyroid hormone levels) who visited the endocrinology department of our institution and (b) available baseline conventional and ASQ ultrasonography data of the thyroid gland (collected as part of our previous study conducted from May to December 2013) [22]. The thyroid status of patients included in this study was discovered during a health checkup or during workup for non-thyroidal illness or neck swelling. All thyroid function tests were repeated 1 month before entering our study to confirm steady state and exclude spontaneous fluctuations. Initially, 120 patients who fulfilled the eligibility criteria and had no focal lesions in the thyroid gland on US were included in the study.

The diagnosis of HT was based on the presence of autoantibodies. HT was confirmed in 10 patients by core needle biopsy (CNB). When thyroiditis-mimicking nodules were detected, careful evaluation of the real-time images was performed to distinguish pseudonodules related to thyroiditis from HT. If the diagnosis was unclear, fine needle aspiration biopsy or CNB was conducted. During follow-up, 10 patients who developed thyroid nodules and 12 patients who underwent any type of thyroidectomy were excluded. We also excluded eight patients who declined to participate in the follow-up evaluations. Follow-up of the participants was conducted for up to 5 years (median 40 [range 3–55] months). A thyroid function test (TFT) was performed at 6-month intervals. We collected demographic and clinical data including sex, age, and hormonal status by review of electronic medical records.

Hormone measurements and follow-up of outcomes

The serum levels of TSH, anti-thyroperoxidase (TPO) antibodies, anti-thyroglobulin (Tg) autoantibodies, free triiodothyronine (T3), and free thyroxine (fT4) were measured at baseline and on each visit by radioimmunoassay using the following reference values: 0.25–4.0 μIU/L for TSH, 0–0.3 U/mL for TPO antibodies, 0–0.3 U/mL for Tg antibodies, 60–190 ng/dL for T3, and 0.89–1.78 ng/dL for fT4. The laboratory evaluation was performed on the same day as the US, and the radiologists who evaluated the images were blinded to the thyroid function status of the patients. The thyroid status of the participants was categorized by an endocrinologist with 23 years of clinical experience (C.H.K.) who was blinded to the US findings. Hypothyroidism describes a condition caused

by inadequate function of the thyroid gland (primary hypothyroidism), inadequate stimulation by TSH (secondary hypothyroidism), or when the hypothalamus is unable to produce sufficient thyrotropin-releasing hormone (TRH) in the brain (tertiary hypothyroidism). Overt hypothyroidism and subclinical hypothyroidism describe the degree of hypothyroidism. Overt hypothyroidism is defined by decreased concentrations of fT4 and elevated serum concentrations of TSH. Subclinical hypothyroidism is a milder form of hypothyroidism, defined as an increased serum TSH level and normal free thyroid hormone levels. The presentation of subclinical hypothyroidism varies, and classic signs and symptoms of hypothyroidism may not be observed. Patients with normal levels of TSH and free thyroid hormones were classified as euthyroid.

The observation period ended if the patient developed overt hypothyroidism or was treated with thyroid hormones for clinical reasons (infertility, hypercholesterolemia, depression). Follow-up studies were carried out at regular 6-month intervals and included full medical and endocrine evaluations.

Imaging evaluations

Thyroid US was performed using an Aplio 500 (Canon Medical Systems) with a 5–12-MHz linear array transducer. All examinations were performed by one of two radiologists (J.Y.L. and H.S.H., with 5 and 25 years of thyroid imaging experience, respectively), who were blinded to the patient's thyroid status. Routine thyroid US was performed first. Then, US images of the longitudinal plane of the thyroid gland were obtained in ASQ mode for 3 s. The display depth (3.5 cm) and transmission focus (1.5 cm) were fixed to keep a constant setting. No patient had enlarged thyroid glands that extended beyond the scanned field.

ASQ

The ASQ software analyzes linear raw data from ultrasound B-mode images and provides parameters that reflect the scattering of echoes in the region of interest (ROI) [24]. The results are shown as occurrences on a modified chi-square distribution histogram. ASQ divides the primary ROI into a large number (up to 1000) of smaller secondary ROIs and displays the C^2-histogram of the distribution of frequency ratios given by the frequency of the ratio. $C^2 = \sigma^2/\sigma R^2$, where σ and σR stand for the standard deviations (SDs) of measured and estimated probability density functions, respectively. [25].

ASQ computes two curves (displayed in red and blue), depending on whether the variation quantitatively changes the σ parameter by less (depicted in red) or more (depicted in blue) than an empirical percentage (20%), respectively. Mode (value with the highest appearance, "peak value"), average, focal disturbance (FD) ratio, and SD are derived from the Cm^2 histogram [26]. If an ideal homogeneous speckle pattern is detected in the ROI, the average and mode values are estimated as 100%, with an extremely narrow range, and the blue curve is flat on the *x*-axis. A homogeneous structure shows a blue curve with a low peak and narrow width, whereas a heterogeneous structure shows a tall and wide blue curve. The FD ratio is increased with higher focal inhomogeneity and lower global homogeneity. The average, mode, blue mode, and blue average are increased if the inhomogeneous area is selected. Details of ASQ are described in the Supplement.

Table 1 Baseline characteristics according to final thyroid status

Variable	Total ($n = 90$)	Progression ($n = 61$)	Non-progression ($n = 29$)	*p* value
Age (years)	47.1 ± 12.3	50.4 ± 11.1	39.2 ± 12.1	< 0.001
No. of male patients (%)	10 (11.1%)	8 (13.1%)	2 (7.9%)	0.38
Thyroid volume (mL)	10.0 ± 7.8	9.5 ± 5.4	10.9 ± 6.8	0.18
Thyroid status				
Subclinical hypothyroid	46 (51.1%)	38 (62.3%)	8 (27.6%)	0.002
Euthyroid	44 (48.9%)	23 (37.7%)	21 (72.4%)	0.001
Qualitative echogenicity	7 (7.8%)	7 (11.5%)	0 (0%)	0.557
Free T4, ng/dL	1.2 ± 0.2	1.3 ± 0.4	1.2 ± 1.9	0.42
T3, ng/dL	152.0 ± 17.4	154.3 ± 18.1	151.3 ± 17.3	0.38
TSH, mIU/L	10.5 ± 12.9	7.5 ± 4.7	3.2 ± 2.3	< 0.001
TPO Ab	60.2 ± 43.2	65.8 ± 40.5	50.0 ± 42.2	0.09
TG Ab	43.2 ± 41.5	51.7 ± 42.4	30.2 ± 34.0	0.01

Data are reported as means ± standard deviation for continuous variables and as frequencies (%) for categorical variables. *p* values were calculated using Student's *t* test or Mann–Whitney *U* test for continuous variables and the chi-square test for categorical variables

TSH thyroid-stimulating hormone, *TPO Ab* anti-thyroid peroxidase antibody, *TG Ab* anti-thyroglobulin antibody

Table 2 Comparison of ASQ parameters between the progression and non-progression groups

ASQ parameter	All patients ($n = 90$)	Progression ($n = 61$)	Non-progression ($n = 29$)	p
Baseline average	120.8 ± 9.5	123.5 ± 10.1	115.3 ± 4.9	< 0.001
Mode	119.7 ± 10.0	119.9 ± 10.4	119.7 ± 9.2	0.91
SD	14.7 ± 2.7	14.9 ± 2.8	14.4 ± 2.7	0.41
Ratio	0.8 ± 0.9	0.8 ± 0.9	0.7 ± 0.9	0.34
Blue average	133.2 ± 13.8	140.1 ± 18.0	138.8 ± 15.9	0.73
Blue mode	139.7 ± 17.2	133.3 ± 14.7	132.9 ± 12.2	0.91
Blue SD	21.0 ± 7.6	21.4 ± 7.7	20.1 ± 7.8	0.47

Data are reported as means ± standard deviation. p values were calculated using Student's t test

ASQ acoustic structure quantification, *SD* standard deviation

Qualitative and quantitative image analyses

Recorded conventional gray-scale images were analyzed qualitatively. Abnormal echogenicity was determined by independent visual inspection by two head-and-neck radiologists (with 5 and 25 years of thyroid imaging experience, respectively), who recorded whether diffuse (homogeneously hypoechoic) or heterogeneous hypoechogenicity (some areas with hypoechogenicity and some areas with normal echogenicity) was evident in the thyroid. Hypoechogenicity was determined to be present if the parenchymal echogenicity was lower than normal in the thyroid parenchyma and submandibular gland. Parenchymal echogenicity was determined by consensus between the two radiologists.

In terms of quantitative ASQ parameters, the B-mode raw data were transferred to an independent workstation, and a rectangular ROI that included the largest possible area of the thyroid parenchyma was drawn for each gland. The peak value in each square centimeter of the histogram for each ROI was calculated from the B-mode raw data using dedicated software (ASQ-R for PC, version 1.0). The calculated ASQ parameters were automatically displayed on the monitor, with parametric maps of the ASQ images. The results were displayed in square-centimeter histograms together with the mode, average, SD, FD ratio, blue mode, blue average, and blue SD. The ASQ values of each lobe were averaged for each patient. ASQ parameters were measured independently by two radiologists (J.Y.L. and H.S.H.) to assess inter-reader agreement, and the values were averaged prior to analysis.

Statistical analysis

All continuous variables were evaluated in terms of normality using the Kolmogorov–Smirnov test. Continuous variables are expressed as means ± SD and categorical variables as numbers with percentages. The patient's clinical features were analyzed and compared according to final thyroid status using the chi-square test for categorical variables and Student's t test for continuous variables. Inter-reader agreement in terms of quantitative ASQ parameters was assessed by calculating intra-class correlation (ICC) coefficients. The extent of agreement was classified using recognized criteria as excellent (ICC > 0.75), fair to good (ICC = 0.40–0.75), or poor (ICC ≤ 0.40).

Development of overt hypothyroidism was defined as low fT4 and high TSH serum levels observed on a TFT and a requirement for fT4 replacement therapy during follow-up. Measured ASQ parameters were averaged prior to analysis, and each ASQ parameter was dichotomized according to the optimal cutoff value derived from receiver operating characteristic curves, in which the sum of the sensitivity and specificity was

Table 3 Thresholds of ASQ parameters and differences in Kaplan–Meier survival curves for each threshold

ASQ parameter	AUROC	ROC threshold	Above threshold*	Below threshold*	p
Average	0.779	> 118	20.5 (67)	46.2 (23)	< 0.001
Mode	0.517	> 120	12.0 (32)	36.0 (58)	0.443
SD	0.583	> 13	12.0 (60)	55.0 (30)	0.015
Ratio	0.620	> 0.29	12.0 (26)	55.0 (64)	< 0.001
Blue average	0.543	> 133	27.0 (64)	29.5 (26)	0.579
Blue mode	0.517	> 131	24.0 (37)	36.0 (53)	0.399
Blue SD	0.568	> 17	24.0 (59)	55.0 (31)	0.138

ASQ acoustic structure quantification, *SD* standard deviation, *ROC* receiver operating characteristic, *AUROC* area under the receiver operating characteristic curve

*Data in parentheses are the numbers of patients, mean survival (median was not obtained)

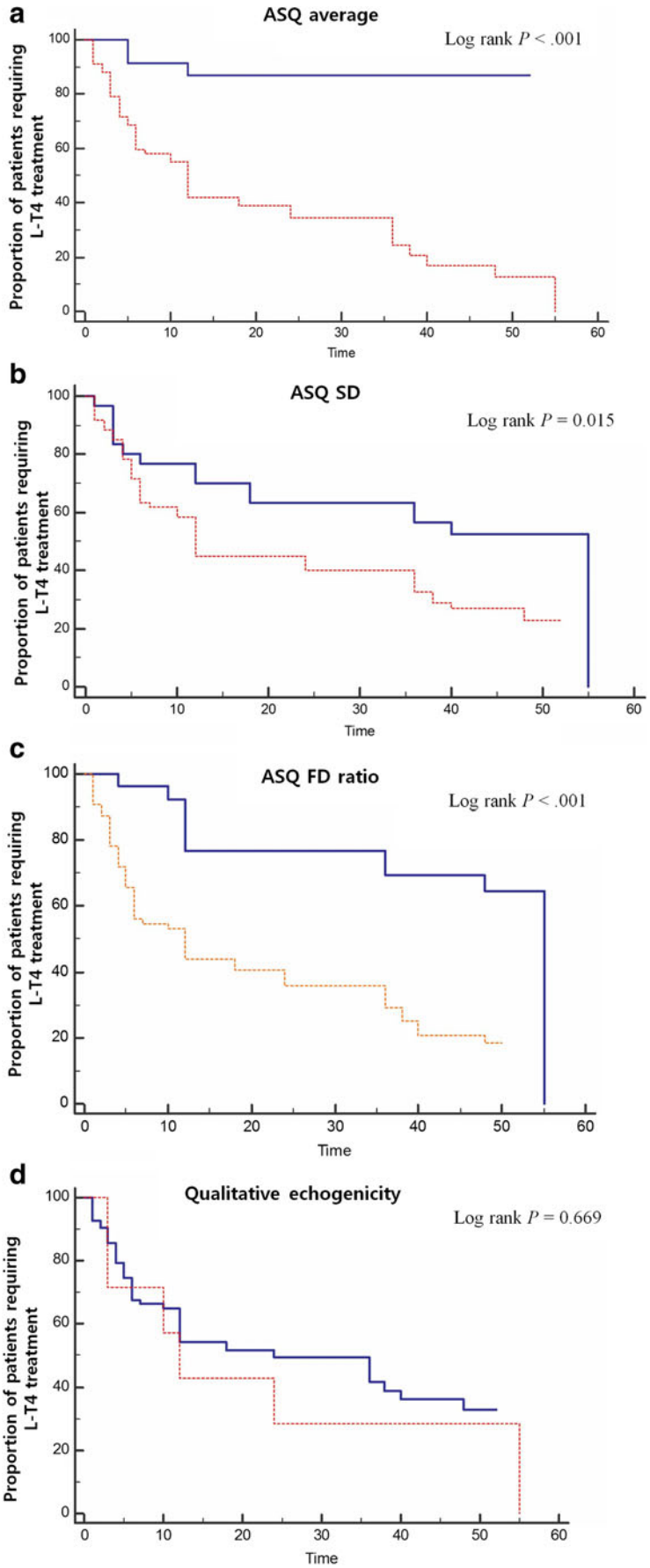

Fig. 1 Kaplan–Meier curves according to (**a**) ASQ average, (**b**) SD, (**c**) FD ratio, and (**d**) qualitative echogenicity. An (**a**) ASQ > 118, (**b**) SD > 13, and (**c**) FD ratio > 0.29 indicated a significantly poorer prognosis of thyroid parenchyma compared with the respective cutoff values (log-rank test $p < 0.001$, $p = 0.015$, and $p < 0.001$, respectively). No significant associations were observed between qualitative echogenicity (**d**) and progression to overt hypothyroidism ($p = 0.669$)

maximized [27], to predict overt hypothyroidism. The unadjusted associations of ASQ parameters and TFT results with development of overt hypothyroidism were evaluated by Kaplan–Meier (KM) analysis, and differences in KM survival curves of patients above versus below each cutoff value were evaluated using a nonparametric log-rank test. Multivariate Cox regression analysis, using the stepwise elimination method, was conducted to determine which parameters were independent predictors of survival. Variables with p values < 0.2 on univariate analysis were used as input variables in multivariate analyses. Spearman rank correlation was performed to determine the correlations between ASQ parameters and TSH and autoantibody levels. All statistical analyses were performed using SPSS (version 22, IBM) and MedCalc (version 18.5, MedCalc Software bvba). A p value < 0.05 was considered to indicate statistical significance.

Results

Patients

The characteristics of the 90 patients are summarized in Table 1. Among the 90 patients (mean age 47.1 ± 12.3 years; range 31–70 years) included in the present study, 10 were male (mean age 46.5 ± 14.2 years; range 38–65 years) and 80 were female (mean age 47.4 ± 11.5 years; range 39–70 years). Of the 90 patients, 61 progressed to overt hypothyroidism by the end of the study (67.7%). The mean time from baseline US to overt hypothyroidism was 27.9 months. The median time to progression was 24.0 months (95% confidence interval [CI] 12.0–38.0).

At baseline, 46 (51.1%) patients were subclinical hypothyroid and 44 (48.9%) were euthyroid. The baseline TSH (p < 0.001) and anti-Tg antibody (p = 0.01) levels were significantly higher in the progression group than in the non-progression group. Thyroid gland volume and serum levels of fT4, T3, and TPO did not show significant differences between the two groups. There was no significant difference in incidence of overt hypothyroidism with regard to sex (median time to progression: males, 12.0 months [95% CI 12.0–40.0]; females, 24.0 months [95% CI 12.0–38.0], p = 0.66). Regarding age, older patients (≥ 42 years) had a significantly shorter time to progression (p = 0.004) than younger patients. In patients ≥ 42 years old, the median and mean times to progression were 12.0 months (95% CI 12.0–36.0) and 23.9 months (95% CI 18.6–29.2), respectively. In patients < 42 years old, the mean time to overt hypothyroidism was 31.2 months (95% CI 24.0–38.3 months).

Table 4 Univariate and multivariate Cox proportional hazards regression analyses for overt hypothyroidism

Variables	HR (95% CI)	p	HR (95% CI)	p
Average	1.05 (1.03, 1.08)	< 0.001	1.03 (1.00, 1.06)	0.037
Mode	1.00 (0.98, 1.03)	0.704		
SD	1.06 (0.96, 1.17)	0.248		
Ratio	1.19 (0.92, 1.54)	0.186		
Blue average	1.00 (0.99, 1.02)	0.796		
Blue mode	1.00 (0.99, 1.02)	0.610		
Blue SD	1.00 (0.96, 1.03)	0.751		
Echogenicity	1.21 (0.48, 3.03)	0.681		
TSH	1.13 (1.07, 1.19)	< 0.001	1.07 (1.00, 1.14)	0.041
TPO Ab	1.00 (1.00, 1.01)	0.238		
Tg Ab	1.01 (1.00, 1.01)	0.002	1.01 (1.00, 1.01)	0.091

HR hazard ratio, *95% CI* 95% confidence interval, *SD* standard deviation, *TSH* thyroid-stimulating hormone, *Tg Ab* anti-thyroglobulin antibody, *TPO Ab* anti-thyroxine peroxidase antibody

Differences in ASQ parameters between patients with progression to overt hypothyroidism and those without progression

The inter-observer agreements in terms of ASQ measurements were nearly perfect for all parameters evaluated (range 0.97–0.98; 95% CI 0.97–0.99). Table 2 shows the summary statistics of the ASQ parameters. Student's t test showed that the baseline ASQ average was significantly higher in the progression group than in the non-progression group (123.5 ± 10.1 vs. 115.3 ± 4.9, p < 0.001). Other ASQ parameters showed higher trends in the non-progression group, but the differences were not statistically significant.

Univariate and multivariate analyses of overt hypothyroidism

Table 3 shows the results of receiver operating characteristic analysis and the optimal cutoff values derived from the curves. The cutoff values of the average, mode, SD, ratio, blue average, blue mode, and blue SD were 118, 120, 13, 0.29, 133, 131, and 17, respectively. The KM curves showed a significantly higher rate of overt hypothyroidism in patients with a higher ASQ average (p < 0.001), SD (p = 0.015), and FD ratio (p < 0.001) than the respective cutoff values (Fig. 1). There were no significant associations of hypoechogenicity on visual analysis (p = 0.669), mode (p = 0.443), blue mode (p = 0.399), blue average (p = 0.579), or blue SD (p = 0.138) with risk of overt hypothyroidism. Subsequent multivariate analysis revealed that the ASQ average (adjusted HR 1.03, p = 0.037) and TSH (HR 1.07, p = 0.041) were independent predictors of overt hypothyroidism in patients with HT. The results of the multivariate Cox regression analysis are shown in Table 4. Representative cases are shown in Figs. 2 and 3.

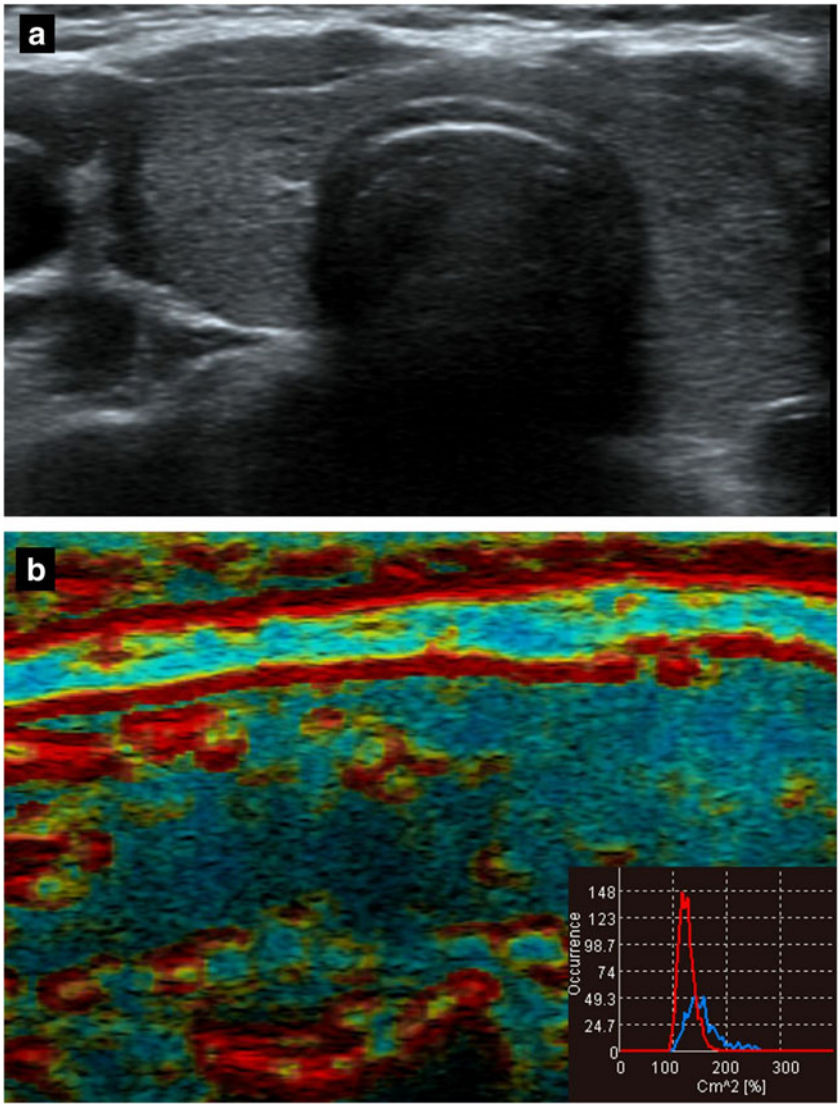

Fig. 2 Initial ultrasonography images of a 47-year-old female with HT who progressed to overt hypothyroidism 3 years later. She had subclinical hypothyroidism at the initial visit. **a** Conventional gray-scale ultrasonography image of the thyroid gland revealed slight coarseness, with decreased parenchymal echogenicity. **b** Parametric ASQ maps revealed heterogeneous areas (red) with deviated, double-peaked, modified chi-squared histograms. The ASQ average increased to 126

Correlation between ASQ and serologic markers

As for the correlations between ASQ and serological markers, moderate correlations were noted between the ASQ average and TSH level ($r = 0.569$, $p < 0.001$). Weak correlations were observed between the ASQ average and TPO antibody ($r = 0.253$, $p = 0.016$) and Tg antibody ($r = 0.289$, $p = 0.006$) levels.

Discussion

In this study, we found that the ASQ average was an independent predictor of overt hypothyroidism in patients with subclinical hypothyroid and euthyroid HT. Specifically, patients with a higher ASQ average (> 118) had a significantly poorer prognosis than the patients with lower values.

In this study, baseline ASQ parameters predicted overt hypothyroidism, whereas visually assessed echogenicity did not. This result indicates that ASQ sensitively detects subtle echo alterations in the parenchyma of patients who already have some degree of follicular destruction and fibrosis resulting in parenchymal hypoechoic lesions, which is also supported by the observation of moderate correlation between ASQ average and the baseline serum TSH level. Therefore, the degree of ASQ elevation may reflect thyroid damage and loss of function, similar to TSH [8]. This is in agreement with previous investigations showing the extent of parenchymal hypoechogenicity in HT reflects the degree of follicular destruction, replaced by inflammatory cell infiltration and fibrosis [12, 13]. In the present study, TSH titers were used to assess the correlation between US and degree of hypothyroidism because TSH reflects the degree of follicular destruction. In earlier studies, constant positive correlation between US findings of hypoechogenicity and degree of hypothyroidism was not demonstrated. In the present study, a positive but

not strong correlation was found between ASQ and TSH, which supports the predictive ability of ASQ.

Normal thyroid parenchyma consists of a three-dimensional arrangement of microstructures that are smaller than the clinical ultrasound wavelength. The statistics of the echo amplitude follow Rayleigh distribution [22, 25]. During disease progression of HT, the fibrotic structures and inflammatory nodules (caused by lymphocytic infiltration) develop and become larger than the wavelength, resulting in a relatively high degree of variance in the scattering cross sections of scatters [24, 25]. A relatively obvious hyperechoic septum and vessel wall contrasts with the hypoechoic inflammatory parenchyma. In this condition, the echotexture is overall coarse and heterogeneous, and the deviation of the echo amplitude distribution from the Rayleigh distribution can be quantified to assess the degree of inflammatory infiltration and fibrosis of the thyroid gland [28]. The current practice for assessing echogenicity in inflamed thyroid tissue is mainly qualitative and based on the operator's experience. Because subtle changes are potentially subject to intra- and inter-observer variabilities, ASQ can provide objective and measurable quantitative information.

Increased serum TSH levels and the presence of TPO antibodies are also predictors of thyroid failure [7, 8, 11]. Baseline serum TSH level is the most important predictor of hypothyroidism progression, followed by autoantibody levels [7–9, 11, 29]. In this study, circulating thyroid autoantibodies were associated with the same or a lower risk of developing overt hypothyroidism as TSH levels, which is in agreement with earlier studies [8, 29]. The present study population with autoimmune thyroiditis already had increased thyroid autoantibody levels, which could explain the obtained results. In this study, ASQ was shown useful for further stratification of patients with autoimmune thyroiditis.

All patients exhibiting subclinical hypothyroidism with serum TSH levels > 10 mIU/L should be treated [30, 31] because they have increased risk of developing overt hypothyroidism and long-term increases in TSH levels are associated with abnormal lipid profiles, endothelial dysfunction, myocardial infarction, and

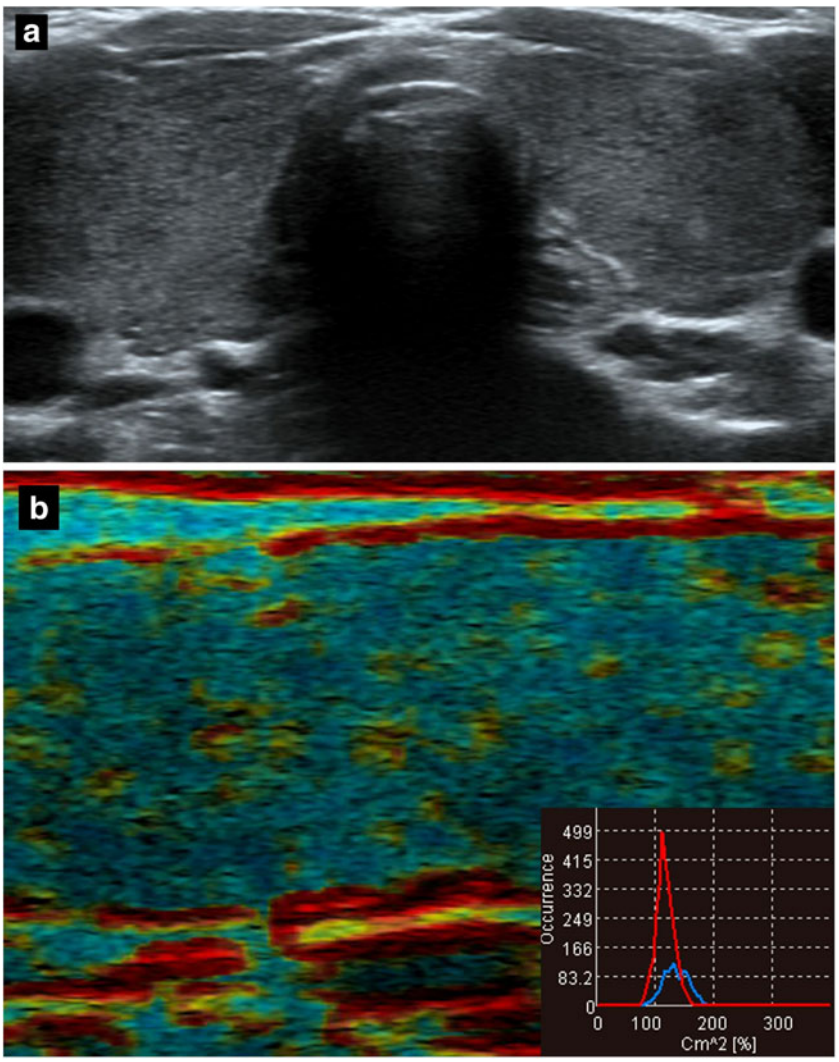

Fig. 3 Initial ultrasonography images of a 31-year-old female with HT. Her subclinical hypothyroid status persisted from the initial visit to the 3-year follow-up. **a** A conventional gray-scale ultrasonography image revealed enlargement of the thyroid gland with patchy hypoechoic areas. **b** Parametric ASQ maps revealed small areas of heterogeneity (yellow and red) with a minimally displaced red curve. The ASQ average was 113

cognitive impairment [32]. In previous studies, levothyroxine replacement was shown to modulate the immune process in animal models and patients with HT [33, 34] and reverse cardiovascular abnormalities and neuropsychiatric symptoms [35]. Hence, the decision to treat patients with subclinical hypothyroidism is dependent on the risk of developing overt hypothyroidism and the different clinical and metabolic conditions mentioned above. In the present study, using ASQ in thyroid US contributed to improved risk assessment when evaluating autoimmune thyroiditis using US. In previous studies, gray-scale US findings of thyroiditis showed an added value for predicting overt hypothyroidism; however, the predictive power was somewhat weaker than serologic markers [15, 16]. Therefore, instead of conventional US, ASQ can be used for better prognostication of patients with HT. High-risk patients stratified with ASQ could undergo more follow-up evaluations using thyroid function tests, and receive timely administration of levothyroxine therapy.

A limitation of this study is the relatively small number of patients, considering the high prevalence of HT. However, the finding that ASQ parameters were significant predictors of overt hypothyroidism, even in this relatively small data set, supports the use of such ultrasound-derived measures compared with traditional risk factors. A second limitation is the lack of generalizability of ASQ imaging since it is a vendor-specific technique. Although good inter-reader, inter-transducer, and inter-platform reproducibility of quantitative US measurements in the liver were demonstrated in previous studies [36–38], whether this technique is applicable to the thyroid gland has not been investigated. In this study, only the potential prognostic value of ASQ imaging was suggested. Third, most patients were diagnosed based on thyroid autoantibody levels, with only a few patients diagnosed histologically. However, serological evaluation of thyroid autoantibody levels is generally accepted as valid in terms of HT diagnosis. Lastly, ASQ parameters were retrospectively analyzed using recorded B-mode raw data; thus, assessment of inter-reader agreement may have been less than optimal.

In conclusion, higher average ASQ values (> 118) were associated with a poorer prognosis in terms of hypothyroidism development. ASQ imaging may have potential as an imaging biomarker along with serological markers in predicting overt hypothyroidism in HT.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Hyun Sook Hong.

Conflict of interest The authors declare that they have no conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent All adult participants provided written informed consent to participate in this study.

Ethical approval Institutional Review Board approval was obtained.

Study subjects or cohorts overlap We disclose that 70 patients in the current study participated in our previous study by Park et al [22]. The previous study dealt with ASQ imaging in terms of differentiating patients with thyroiditis from normal subjects. In this study, those patients were followed up for 5 years, and the prognostic utility of ASQ was investigated.

Methodology
- prospective
- Diagnostic or prognostic study
- performed at one institution

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