

IMPACT OF VIRAL HEPATITIS AND THYROID AUTOANTIBODIES ON TUMOR AGGRESSIVENESS IN PAPILLARY THYROID CARCINOMA

Gökçen Güngör Semiz^{1*}, Sabay Akbaş¹, Selda Arslan¹, Şeyhmus Abakay¹, Guljahan Hatamova¹, Ahmet Ömer İkiz², Merih Güray Durak³, Hüseyin Salih Semiz⁴, Hülya Ellidokuz⁵, Özhan Özdoğan⁶, Abdurrahman Çömlekçi¹

¹ Dokuz Eylül University, Faculty of Medicine, Department of Internal Medicine, Division of Endocrinology and Metabolism, İzmir, Türkiye

² Dokuz Eylül University, Faculty of Medicine, Department of Ear, Nose, Throat and Head and Neck Surgery, İzmir, Türkiye

³ Dokuz Eylül University, Faculty of Medicine, Department of Pathology, İzmir, Türkiye

⁴ Dokuz Eylül University, Institute of Oncology, Department of Medical Oncology, İzmir, Türkiye

⁵ Dokuz Eylül University, Institute of Oncology, Department of Preventive Oncology, İzmir, Türkiye

⁶ Dokuz Eylül University, Faculty of Medicine, Department of Nuclear Medicine, İzmir, Türkiye

ORCID: G.G.S. 0000-0002-8915-9178; S.A. 0000-0003-4094-6450; S.A. 0009-0004-4210-7348; Ş.A. 0000-0002-0049-2020; G.H. 0000-0002-1372-4978; A.Ö.İ. 0000-0002-1636-9457; M.D. 0000-0003-3516-952X; H.S.S. 0000-0002-7083-8517; H.E. 0000-0001-8503-061X; Ö.Ö. 0000-0002-3357-4778; A.Ç. 0000-0002-3135-2127

*Corresponding Author: Gökçen Güngör Semiz, e-mail: ggungor28@hotmail.com

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ABSTRACT

Background and Purpose: To evaluate whether hepatitis B (HBV) or C (HCV) seropositivity and thyroid autoimmunity are associated with aggressive histopathological features of papillary thyroid carcinoma (PTC).

Methods: Retrospective cohort study of 521 patients with histologically confirmed PTC. HBV serology was available in 289 patients, HCV in 292, anti-TPO in 175 and anti-Tg in 208 (complete-case analyses). Subgroups by serostatus, age, sex and autoantibody status were compared with odds ratios (ORs) and 95% confidence intervals (CIs), and an exploratory multivariable model was fitted for extrathyroidal extension (ETE).

Results: Twelve of 289 tested patients (4.2%) were HBsAg-positive and 4 of 292 (1.4%) anti-HCV-positive. No association was detected between viral seropositivity and aggressive features (minimum detectable OR ≥ 4.6). Age ≤ 55 years was associated with central lymph node metastasis (OR 2.42, 95% CI 1.33–4.41), and anti-TPO and anti-Tg positivity with ETE (OR 3.53, 0.97–12.76; OR 2.88, 1.07–7.79); anti-TPO also with capsular invasion (OR 2.25, 1.11–4.57). After adjustment, none remained significant.

Conclusion: In this cohort, no statistically significant association was detected between HBV or HCV seropositivity and aggressive clinicopathological features; given the small seropositive subgroups, this is not evidence of absence. Younger age and thyroid autoimmunity were not independent predictors.

Key words: Papillary Thyroid Carcinoma; Hepatitis B; Hepatitis C; Thyroid Autoimmunity; Tumor Aggressiveness.

INTRODUCTION

Thyroid carcinomas are the most common among endocrine malignancies, and differentiated thyroid carcinomas represent the most frequently observed type of thyroid cancer (1,2). Among differentiated thyroid tumors, papillary thyroid carcinoma is the most frequently encountered subtype. Papillary thyroid carcinoma (PTC) is generally known for its indolent clinical course and excellent long-term survival rates (3). However, a subset of patients diagnosed with PTC exhibit aggressive histopathological features—such as bilaterality, multifocality, extrathyroidal extension, lymphovascular invasion, and particularly regional lymph node metastasis—which negatively impact prognosis by increasing the risk of recurrence.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are chronic infectious agents that affect millions of individuals worldwide and are primarily responsible for the development of cirrhosis and hepatocellular carcinoma. Their prevalence rates vary significantly across regions of the world (4). According to the nationwide, large-scale TURHEP field study, the seroprevalence of hepatitis B surface antigen (HBsAg) and hepatitis C antibody [anti-HCV] in the general population in Turkey is reported to be approximately 4% and 1%, respectively. Prevalence rates also vary across regions in our country (5). A review of the literature reveals that both HBV and HCV positivity affect numerous extrahepatic organs and systems, serve as risk factors for various malignancies, and can induce autoimmune diseases (6-8). Studies indicate that some viruses may affect the occurrence, progression, and prognosis of thyroid carcinoma. Accordingly, the association between thyroid carcinomas and Epstein-Barr virus (EBV), human immunodeficiency virus (HIV), human papillomavirus (HPV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and HCV has been investigated (9,10,11). Although the relationship between HBV and PTC has been explored in a limited number of studies, available evidence indicates significantly higher rates of central lymph node metastasis and bilaterality among HBV-positive patients with papillary thyroid carcinoma (4). Additionally, while previous research on the relationship between viral infections and thyroid carcinoma has predominantly treated thyroid malignancies as a single, broad category, studies specifically focusing on papillary thyroid carcinoma remain

scarce. To address this gap in the literature, this study aimed to evaluate the association of preoperative HBV and HCV seropositivity with the histopathological features of PTC at initial diagnosis.

MATERIALS AND METHODS

Study Design and Patient Population

This retrospective cohort (chart-review) study included patients with papillary thyroid carcinoma (PTC) who were managed in the Endocrinology and Oncology departments between January 2010 and January 2022. Clinical and histopathological data were retrospectively extracted from the hospital's electronic medical records (EMR). The study protocol was approved by the Institutional Review Board of XXXXXX (Approval No:2022/16-14; Approval Date: 27 April 2022). The approval covered the retrospective review of patient records from 2010 to 2022; the entire study period therefore falls within the approved period. Patients were included based on the following criteria: (i) age >18 years; (ii) histopathologically confirmed diagnosis of PTC; (iii) prior total thyroidectomy; and (iv) available preoperative serological data for HBV and HCV. Conversely, patients were excluded if they met any of the following criteria: (i) age < 18 years; (ii) histopathological diagnosis of benign thyroid lesions or non-PTC malignancies; and (iii) incomplete clinicopathological data or surgery performed at external centers.

Data Collection and Study Variables

Demographic, histopathological, and preoperative laboratory data were collected for all patients. Laboratory parameters included serum thyroid-stimulating hormone (TSH), thyroid autoantibodies (anti-thyroid peroxidase [anti-TPO] and anti-thyroglobulin [anti-Tg]), and a viral hepatitis panel (hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core immunoglobulin G [anti-HBc IgG], and hepatitis C antibody [anti-HCV]).

Histopathological parameters extracted from surgical reports included the specific PTC subtype (e.g., classical, follicular variant, tall cell...), maximum tumor diameter, surgical margin status, multifocality, bilaterality, capsular invasion, extrathyroidal extension (ETE), and distant metastasis at diagnosis (M-stage). Data regarding

lymph node metastasis (LNM) included its presence, the involved compartment (central vs. lateral), and the number of metastatic nodes.

Pathological tumor staging was performed according to the American Joint Committee on Cancer (AJCC) TNM classification, 8th edition, which took effect in January 2018 and therefore applied to the later part of the study period; the 55-year threshold introduced in that edition was adopted for staging, and the age-stratified analyses compared patients aged 55 years or younger with those older than 55 years (patients aged exactly 55 years, $n = 15$, were assigned to the younger group). ETE was defined as any extrathyroidal extension — microscopic or gross — documented in the definitive histopathology report. In line with the 8th edition, gross ETE invading only the strap muscles was staged as T3b and invasion of major neck structures as T4a/T4b, whereas microscopic ETE alone did not alter the T stage. The terms “extrathyroidal invasion” and “extrathyroidal extension”, used interchangeably in the previous version, refer to the same finding; “extrathyroidal extension (ETE)” is now used consistently throughout. Central and/or lateral neck dissection was not performed routinely; dissection was therapeutic, being undertaken only in patients with lymph nodes considered suspicious on preoperative neck ultrasonography — with fine-needle aspiration confirmation when indicated — or macroscopically suspicious at surgery, whereas prophylactic central neck dissection was not performed in clinically node-negative (cN0) patients. Reported CLNM and LLNM rates therefore reflect pathologically confirmed metastases among dissected patients and should not be interpreted as the prevalence of occult nodal disease in the whole cohort. Thyroid autoimmunity was defined serologically as anti-TPO and/or anti-Tg positivity above the laboratory reference limit (anti-TPO > 13.8 IU/mL; anti-Tg > 4.5 U/mL); a histopathological diagnosis of Hashimoto's thyroiditis was not required.

HBV-naïve patients were defined as those who were HBsAg-negative, anti-HBc IgG-negative, and anti-HBs-negative. Resolved HBV infection was defined by HBsAg negativity and anti-HBc IgG positivity, with or without anti-HBs positivity. HBsAg positivity was taken to indicate current (chronic) HBV infection; HBV DNA levels and HBeAg status were not available in the medical

records. Anti-HCV positivity indicates previous exposure to HCV and does not by itself establish active infection; HCV RNA results were not available for the anti-HCV-positive patients, so active HCV infection could not be confirmed.

Statistical Analysis

All data analyses were executed using IBM SPSS Statistics software for Windows (version 32.0). Baseline cohort characteristics were summarized using counts and proportions for categorical variables, and means $\pm$ standard deviations for continuous variables. The distribution patterns of continuous datasets were verified through Shapiro-Wilk and Kolmogorov-Smirnov tests. Based on these normality checks, inter-group differences were computed employing either the non-parametric Mann-Whitney U test or the unpaired t-test. Associations between categorical variables were examined via Fisher's exact test or Pearson's chi-square test, dictated by expected frequencies. Fisher's exact test was applied whenever any expected cell count was below five—as was the case for most comparisons involving the small HBsAg-positive and anti-HCV-positive subgroups—and the test used for each comparison is indicated in the table footnotes. Unadjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for 2 $\times$ 2 comparisons; the Haldane–Anscombe correction (0.5 added to each cell) was applied when a cell contained zero events. For borderline chi-square results involving the small seropositive subgroups, Fisher's exact test was additionally reported as a sensitivity analysis. To elucidate the influence of viral serology and host-related factors on tumor aggressiveness, the study population was stratified by demographic features (sex; age ≤ 55 vs. > 55 years), autoimmune profiles (anti-TPO/anti-Tg presence), and viral hepatitis status (anti-HCV positivity, resolved HBV status, and HBsAg positivity). Serological and autoantibody data were available for subsets of the cohort (HBV, 289/521; HCV, 292/521; anti-TPO, 175/521; anti-Tg, 208/521); analyses followed a complete-case approach, and the valid denominator for each analysis is indicated in the corresponding table. To assess potential selection bias arising from non-systematic serological testing, baseline demographic and histopathological characteristics of tested and untested patients were compared

(Supplementary Table S1). The primary exposures were HBsAg and anti-HCV seropositivity, and the prespecified outcomes comprised six individual histopathological aggressiveness indicators (multifocality, bilaterality, capsular invasion, ETE, CLNM, and LLNM); no composite endpoint was defined, and these indicators were analyzed separately because their prognostic weights differ. Analyses of demographic subgroups and thyroid autoantibodies were exploratory. No formal adjustment for multiple testing was applied; given the number of comparisons performed, nominally significant results ($p < 0.05$) should be regarded as hypothesis-generating. Because the number of seropositive patients was fixed by the available cohort, a post-hoc sensitivity analysis estimated the minimum detectable effect size: with a two-sided α of 0.05 and 80% power, the smallest detectable odds ratios were approximately 4.6 for common outcomes (e.g., multifocality) and ≥ 10 for infrequent outcomes (e.g., CLNM, ETE) in the HBsAg comparisons (12 vs. 277), and ≥ 10 for all anti-HCV comparisons (4 vs. 288). Accordingly, non-significant results should not be interpreted as evidence of absence of an effect. Furthermore, an exploratory multivariable binary logistic regression model—including age, sex, maximum tumor diameter, anti-TPO positivity, and anti-Tg positivity—was constructed to examine independent determinants of extrathyroidal extension (ETE); the full model estimates are presented in Table 7. Given the small number of ETE events among patients with complete covariate data, the model is prone to overfitting and its results are presented as exploratory. Separate multivariable models for HBsAg or anti-HCV serostatus were not fitted: with 12 HBsAg-positive and 4 anti-HCV-positive patients, and correspondingly few outcome events in these subgroups, the number of events per candidate variable was far below the conventional minimum of ten, so any such model would have been uninterpretable. The viral hepatitis comparisons are therefore reported as unadjusted analyses with odds ratios and 95% confidence intervals. The threshold for statistical significance was defined as a two-tailed alpha level of 0.05 or lower.

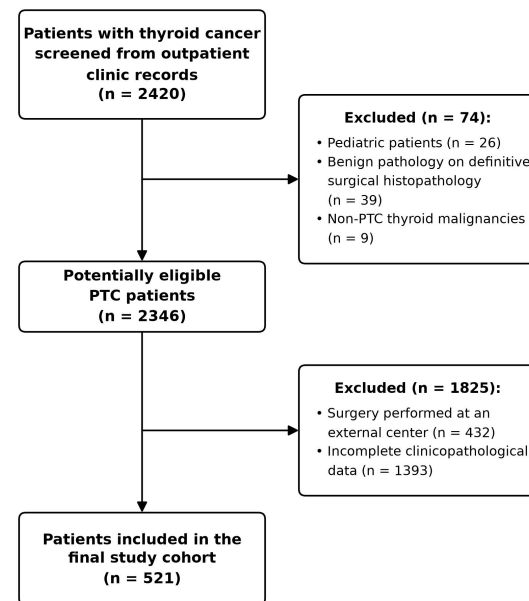


Figure 1. Flowchart of the study design and patient selection process. Exclusions due to external-center surgery ($n = 432$) and incomplete clinicopathological data ($n = 1393$) are shown separately. (Abbreviations: PTC: papillary thyroid carcinoma.)

RESULTS

Study Population and Clinicopathological Characteristics

A total of 2420 patients with outpatient clinic (Endocrinology, Nuclear Medicine and Oncology) records diagnosed with thyroid cancer during the study period were screened. Following the initial evaluation, 26 pediatric patients, 39 patients in whom a thyroid-cancer diagnostic code had been entered in error and whose definitive surgical pathology revealed benign disease, and 9 patients with non-PTC thyroid malignancies were excluded from the dataset. Furthermore, 1825 patients were excluded because surgery had been performed at an external center ($n = 432$) or because of incomplete clinicopathological data, including unavailable definitive histopathology reports ($n = 1393$). In accordance with the inclusion and exclusion criteria, a total of 521 patients were included in the study (Fig. 1).

Table 1. Baseline characteristics of the study population (n = 521)

Characteristic	n (%) or value
Age (years), mean $\pm$ SD / median (min–max)	56.9 $\pm$ 14.3 / 59 (20–94)
Age $\leq$ 55 years	222 (42.6)
Age > 55 years	299 (57.4)
Sex, female	381 (73.1)
Sex, male	140 (26.9)
Pre-operative TSH (mIU/L), mean $\pm$ SD / median (min–max)*	1.9 $\pm$ 2.4 / 1.4 (0.0–32.0)
Anti-TPO positive	104 (20.0)
Anti-TPO negative	71 (13.6)
Anti-TPO not tested	346 (66.4)
Anti-Tg positive	78 (15.0)
Anti-Tg negative	130 (25.0)
Anti-Tg not tested	313 (60.1)
HBsAg positive	12 (2.3)
HBsAg negative	277 (53.2)
HBsAg not tested	232 (44.5)
Resolved HBV infection†	20 (3.8)
Anti-HCV positive	4 (0.8)
Anti-HCV negative	288 (55.3)
Anti-HCV not tested	229 (44.0)

Percentages refer to the full cohort (n = 521). Serological and autoantibody testing was not performed systematically; the “not tested” counts are therefore given explicitly for every marker. * Pre-operative TSH was available in 416 patients. † Resolved HBV infection: HBsAg (–), anti-HBs (+/–) and anti-HBc IgG (+); corresponds to 6.9% of the 289 patients with available HBV serology. Abbreviations: SD: standard deviation; TSH: thyroid-stimulating hormone; Anti-TPO: anti-thyroid peroxidase antibody; Anti-Tg: anti-thyroglobulin antibody; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; Anti-HCV: hepatitis C virus antibody.

Among the included cohort, 381 (73.1%) were female, and 140 (26.9%) were male, with a mean age of 56.93 ± 14.30 years (range: 20–94 years). Among the 521 included patients, 207 (39.7%) were diagnosed with papillary thyroid microcarcinoma, whereas 314 (60.3%) had tumors larger than 1 cm. The specific histological subtypes of papillary carcinoma, along with other baseline descriptive characteristics, are summarized in Table 1. Within this cohort, preoperative HBV serological screening was documented in 289 patients, while 232 patients lacked HBV serology. Among those evaluated, 12 patients (4.2%) tested positive for HBsAg. Additionally, 20 patients (6.9%) showed serological evidence of resolved HBV infection (testing negative for HBsAg and positive for anti-HBc IgG, regardless of anti-HBs status). Pre-operative HCV serology was evaluated in 292 patients, whereas 229 patients were not tested. Among the screened group, 4 patients (1.4%) were positive for Anti-HCV. Consequently, definitive statistical and clinicopathological comparative analyses were conducted on these analyzed subsets with available pre-operative serological data. Baseline and histopathological characteristics of patients with and without available serology are compared in Supplementary Table S1. The two groups were comparable in age, sex, tumor size, multifocality,

bilaterality, capsular invasion, CLNM, LLNM and M1 status, but patients without preoperative serology had significantly higher rates of lymphovascular invasion (13.6% vs. 4.5%; $p < 0.001$), extrathyroidal extension (11.9% vs. 4.5%; $p = 0.002$) and pathological N1 disease (12.6% vs. 7.3%; $p = 0.040$).

Among the histological subtypes of papillary carcinoma, the classical (53.9%) and follicular variants (24%) predominated, and the coexistence of both classical and follicular features was observed in 9.2% of patients.

These were followed by the oncocytic variant (8.3%), whereas aggressive histologies, including tall-cell, solid, and diffuse sclerosing variants, were extremely rare. In the study cohort, papillary thyroid microcarcinomas accounted for 39.7% ($n = 207$) of the tumors. Based on definitive surgical pathology reports, the mean maximum tumor diameter was 16.4 ± 14.0 mm, with a median of 12 mm (range: 0.5–95 mm). Analysis of tumor aggressiveness features revealed multifocal tumor foci in 48.0% ($n = 250$) of the patients and bilateral involvement in 42.4% ($n = 221$). Tumor capsular invasion was present in 23.8% ($n = 124$) of the cases, while extrathyroidal extension (ETE) was observed in 7.7% ($n = 40$). At the time of initial diagnosis, central lymph node metastasis (CLNM) was detected in 9.6% ($n = 50$) of the patients, and lateral lymph node metastasis (LLNM) in 7.5% (n

= 39), culminating in an overall pathological regional lymph node metastasis (N1 stage) rate of 9.6% (n = 50). Distant organ metastasis (M1) at initial presentation was documented in only 1.5% (n = 8) of the study population. Regarding the sites of distant metastasis, the lung was the most frequently involved organ (n = 6), followed by bone (n = 1) and one further site (n = 1). The baseline clinicopathological and histopathological characteristics of the study cohort are summarized in Table 2.

Association of HBV and HCV Seropositivity with Tumor Aggressiveness

A clinicopathological comparison was performed between pre-operative HBsAg-positive (n = 12) and HBsAg-negative (n = 277) patients. No significant differences were observed in the rates of multifocality, extrathyroidal extension, or capsular invasion.

Likewise, the rates of lymphovascular and perineural invasion were similar between the groups. There was also no significant difference in central or lateral lymph node metastasis or in the overall N1 stage. The bilaterality rate was lower in HBsAg-positive than in HBsAg-negative patients (16.7% vs. 46.9%; OR 0.23, 95% CI 0.05–1.05; chi-square $p = 0.039$; Fisher's exact test as a sensitivity analysis, $p = 0.072$); given the small subgroup size, this isolated borderline finding should be interpreted with caution. Furthermore, patients with resolved HBV infection were compared with HBV-naïve patients. In this comparison the two groups were similar for tumor size, multifocality, bilaterality, lymphovascular and perineural invasion, ETE, CLNM, LLNM and pathological N stage, but capsular invasion was more frequent among patients with resolved infection (30.0% vs. 11.0%; OR 3.46, 95% CI 1.14–10.45; Fisher's exact $p = 0.033$).

Table 2. Distribution of clinicopathological and histopathological features of the study cohort (n = 521)

Characteristic	n (%) or value
Tumor diameter (mm)*, mean $\pm$ SD / median (min–max)	16.4 $\pm$ 14.0 / 12 (0.5–95)
Tumor size $\leq$ 1.0 cm	207 (39.7)
Tumor size > 1.0 cm	314 (60.3)
Histological subtype: classical	281 (53.9)
Histological subtype: follicular	125 (24.0)
Histological subtype: classical + follicular	48 (9.2)
Histological subtype: oncocytic	43 (8.3)
Histological subtype: tall cell	4 (0.8)
Histological subtype: solid	2 (0.4)
Histological subtype: diffuse sclerosing	1 (0.2)
Histological subtype: not specified	17 (3.3)
Surgical margin: negative	466 (89.4)
Surgical margin: positive	39 (7.5)
Surgical margin: not reported	16 (3.1)
Pathological T stage: T1	362 (69.5)
Pathological T stage: T2	121 (23.2)
Pathological T stage: T3	35 (6.7)
Pathological T stage: T4	2 (0.4)
Pathological T stage: not available	1 (0.2)
Pathological N stage: N0	469 (90.0)
Pathological N stage: N1	50 (9.6)
Pathological N stage: not available	2 (0.4)
M stage: M0	511 (98.1)
M stage: M1	8 (1.5)
M stage: not available	2 (0.4)
Bilaterality	221 (42.4)
Multifocality	250 (48.0)
Capsular invasion	124 (23.8)
Lymphovascular invasion	44 (8.4)
Perineural invasion	6 (1.2)
Extrathyroidal extension (ETE)	40 (7.7)
CLNM	50 (9.6)
LLNM	39 (7.5)

* Tumor diameter refers to the maximum dimension of the primary tumor focus and was available in 518 patients. All variables are reported against the full cohort (n = 521); categories for missing or unspecified data are shown explicitly so that every variable sums to 521. Missing values for the remaining features were: bilaterality 4, multifocality 5, capsular invasion 9, lymphovascular invasion 4, perineural invasion 6, ETE 5, CLNM 4 and LLNM 4. Abbreviations: CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; ETE: extrathyroidal extension; SD: standard deviation.

Table 3. Association between HBV serological status and histopathological aggressiveness in papillary thyroid carcinoma

Histopathological feature	HBsAg negative	HBsAg positive	OR (95% CI)†	p‡	Resolved HBV§	HBV-naïve§	OR (95% CI)†	p‡
Tumor size ≥ 1 cm	174/277 (62.8)	8/12 (66.7)	1.18 (0.35–4.03)	1.000 F	15/20 (75.0)	87/129 (67.4)	1.45 (0.49–4.25)	0.499 C
Pathological N1	20/277 (7.2)	1/12 (8.3)	1.17 (0.14–9.51)	0.603 F	1/20 (5.0)	9/129 (7.0)	0.70 (0.08–5.86)	1.000 F
Multifocality	146/277 (52.7)	4/12 (33.3)	0.45 (0.13–1.52)	0.188 C	9/20 (45.0)	69/129 (53.5)	0.71 (0.28–1.83)	0.479 C
Bilaterality	130/277 (46.9)	2/12 (16.7)	0.23 (0.05–1.05)	0.039 C ¶	11/20 (55.0)	56/129 (43.4)	1.59 (0.62–4.11)	0.332 C
Capsular invasion	63/275 (22.9)	5/12 (41.7)	2.40 (0.74–7.83)	0.163 F	6/20 (30.0)	14/127 (11.0)	3.46 (1.14–10.45)	0.033 F
Lymphovascular invasion	13/277 (4.7)	0/12 (0.0)	—	1.000 F	1/20 (5.0)	7/129 (5.4)	0.92 (0.11–7.88)	1.000 F
Perineural invasion	2/277 (0.7)	0/12 (0.0)	—	1.000 F	0/20 (0.0)	1/129 (0.8)	—	1.000 F
ETE	13/277 (4.7)	0/12 (0.0)	—	1.000 F	0/20 (0.0)	6/129 (4.7)	—	1.000 F
CLNM	24/277 (8.7)	0/12 (0.0)	—	0.608 F	1/20 (5.0)	13/129 (10.1)	0.47 (0.06–3.80)	0.694 F
LLNM	17/277 (6.1)	1/12 (8.3)	1.39 (0.17–11.41)	0.545 F	1/20 (5.0)	7/129 (5.4)	0.92 (0.11–7.88)	1.000 F

Data are expressed as n/valid N (%); denominators differ slightly between rows because of variable-specific missing data. Bold p-values indicate statistical significance ($p < 0.05$). † Unadjusted odds ratio (HBsAg-positive vs. -negative; resolved vs. naïve). The Haldane–Anscombe correction (0.5 added to each cell) was applied when a cell contained no events; “—” indicates that the estimate was not interpretable because one group had no events. ‡ C: Pearson’s chi-square test (all expected counts ≥ 5); F: Fisher’s exact test (any expected count < 5). The test used is indicated next to each p-value. ¶ Bilaterality, HBsAg-positive vs. -negative: the minimum expected count was 5.5, so Pearson’s chi-square test applies under the prespecified rule ($p = 0.039$). As a sensitivity analysis, Fisher’s exact test gives $p = 0.072$; given the very small HBsAg-positive subgroup ($n = 12$) this isolated result is interpreted with caution. § Resolved HBV infection: HBsAg (–), anti-HBs (+/–), anti-HBc IgG (+), $n = 20$. HBV-naïve: HBsAg (–), anti-HBs (–) and anti-HBc IgG (–), $n = 129$. Patients with isolated anti-HBs positivity (vaccine-induced immunity) were not included in either group. Abbreviations: CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; ETE: extrathyroidal extension; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; OR: odds ratio; CI: confidence interval.

Given the small resolved-infection subgroup ($n = 20$) and the number of comparisons performed, this isolated finding should be regarded as hypothesis-generating.

Similarly, pre-operative Anti-HCV-negative and Anti-HCV-positive patients were compared clinicopathologically. No significant differences were observed regarding the rates of multifocality or bilaterality. Furthermore, the incidences of extrathyroidal extension, capsular invasion, lymphovascular invasion, and perineural invasion were comparable between the two groups. Finally, no significant differences were found in the rates of central and lateral lymph node metastasis or the overall pathological N1 stage. The relationships between viral hepatitis serostatus (HBV and HCV) and tumor aggressiveness are detailed in Table 3 and Table 4, respectively.

Impact of Host Demographics and Background Thyroid Autoimmunity

The study cohort was further evaluated regarding demographic characteristics and background thyroid autoimmunity. While no significant differences in tumor aggressiveness were observed between sexes, age-stratified analyses (≤ 55 vs. > 55 years) demonstrated that patients aged 55 years or younger had significantly higher rates of central lymph node metastasis (CLNM; 14.2% vs. 6.4%; OR 2.42, 95% CI 1.33–4.41; $p = 0.003$) and overall pathological N1 stage (12.7% vs. 7.4%; OR 1.82, 95% CI 1.01–3.28; $p = 0.044$). Regarding background autoimmunity, univariable analyses revealed that both anti-TPO and anti-Tg positivity were associated with extrathyroidal extension (ETE) (13.5% vs. 4.2%; OR 3.53, 95% CI 0.97–12.76; $p = 0.043$, and 14.1% vs. 5.4%; OR

2.88, 95% CI 1.07–7.79; $p = 0.030$, respectively). Additionally, anti-TPO positivity was associated with significantly higher rates of tumor capsular invasion (35.6% vs. 19.7%; OR 2.25, 95% CI 1.11–4.57; $p = 0.023$), whereas anti-Tg positivity was associated with a significantly lower proportion of tumors measuring >1 cm (51.3% vs. 66.2%; OR 0.54, 95% CI 0.30–0.96; $p = 0.034$).

The stratified analyses of tumor aggressiveness features by age and sex and by thyroid autoantibody status are presented in Tables 5 and 6, respectively. To determine whether the variables identified as significant in univariable analyses act as independent risk factors for ETE, a multivariable binary logistic regression model was constructed; the full model estimates (ORs, 95% CIs, and p -values) are presented in Table 7.

Table 4. Association between HCV serological status and histopathological aggressiveness in papillary thyroid carcinoma

Histopathological feature	Anti-HCV negative	Anti-HCV positive	OR (95% CI)†	p ‡
Tumor size ≥ 1 cm	172/288 (59.7)	3/4 (75.0)	2.02 (0.21–19.69)	0.652 F
Pathological N1	24/288 (8.3)	0/4 (0.0)	—	1.000 F
Multifocality	149/288 (51.7)	1/4 (25.0)	0.31 (0.03–3.02)	0.359 F
Bilaterality	132/288 (45.8)	1/4 (25.0)	0.39 (0.04–3.83)	0.628 F
Capsular invasion	66/286 (23.1)	2/4 (50.0)	3.33 (0.46–24.12)	0.235 F
Lymphovascular invasion	16/288 (5.6)	0/4 (0.0)	—	1.000 F
Perineural invasion	2/288 (0.7)	0/4 (0.0)	—	1.000 F
ETE	15/288 (5.2)	0/4 (0.0)	—	1.000 F
CLNM	26/288 (9.0)	0/4 (0.0)	—	1.000 F
LLNM	21/288 (7.3)	0/4 (0.0)	—	1.000 F

Data are expressed as n/valid N (%). Because only four patients were anti-HCV-positive, every comparison used Fisher's exact test and all results are descriptive and hypothesis-generating only. † Unadjusted odds ratio (anti-HCV-positive vs. -negative), with the Haldane–Anscombe correction where a cell contained no events; "—" indicates that the estimate was not interpretable. ‡ F: Fisher's exact test. Abbreviations: CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; ETE: extrathyroidal extension; Anti-HCV: hepatitis C virus antibody; OR: odds ratio; CI: confidence interval.

Table 5. Stratified analysis of tumor aggressiveness features by age and sex

Feature	Age ≤ 55 years	Age > 55 years	OR (95% CI)†	p ‡	Male	Female	OR (95% CI)†	p ‡
Tumor size ≥ 1 cm	134/222 (60.4)	180/299 (60.2)	1.01 (0.71–1.44)	0.971 C	90/140 (64.3)	224/381 (58.8)	1.26 (0.84–1.88)	0.256 C
Pathological N1	28/221 (12.7)	22/298 (7.4)	1.82 (1.01–3.28)	0.044 C	18/139 (12.9)	32/380 (8.4)	1.62 (0.88–2.99)	0.122 C
Multifocality	107/218 (49.1)	143/298 (48.0)	1.04 (0.74–1.48)	0.806 C	67/139 (48.2)	183/377 (48.5)	0.99 (0.67–1.46)	0.945 C
Bilaterality	91/219 (41.6)	130/298 (43.6)	0.92 (0.65–1.31)	0.638 C	60/139 (43.2)	161/378 (42.6)	1.02 (0.69–1.52)	0.907 C
Capsular invasion	49/216 (22.7)	75/296 (25.3)	0.86 (0.57–1.31)	0.489 C	38/137 (27.7)	86/375 (22.9)	1.29 (0.83–2.01)	0.261 C
ETE	21/218 (9.6)	19/298 (6.4)	1.57 (0.82–2.99)	0.172 C	15/139 (10.8)	25/377 (6.6)	1.70 (0.87–3.34)	0.117 C
CLNM	31/219 (14.2)	19/298 (6.4)	2.42 (1.33–4.41)	0.003 C	14/139 (10.1)	36/378 (9.5)	1.06 (0.56–2.04)	0.852 C
LLNM	20/219 (9.1)	19/298 (6.4)	1.48 (0.77–2.84)	0.241 C	15/139 (10.8)	24/378 (6.3)	1.78 (0.91–3.51)	0.090 C
HBsAg positivity§	6/121 (5.0)	6/168 (3.6)	1.41 (0.44–4.48)	0.560 C	4/79 (5.1)	8/210 (3.8)	1.35 (0.39–4.60)	0.741 F
Anti-HCV positivity§	0/120 (0.0)	4/172 (2.3)	—	0.146 F	1/78 (1.3)	3/214 (1.4)	0.91 (0.09–8.91)	1.000 F

Data are expressed as n/valid N (%); denominators differ between rows because of variable-specific missing data. Bold p -values indicate statistical significance ($p < 0.05$). Patients aged exactly 55 years ($n = 15$) were assigned to the younger group; the strata are therefore ≤ 55 and > 55 years. † Unadjusted odds ratio (≤ 55 vs. > 55 years; male vs. female). ‡ C: Pearson's chi-square test; F: Fisher's exact test (any expected count < 5). § Serology rows are restricted to patients with the corresponding test available; the denominator shown is the number tested within each stratum. Abbreviations: CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; ETE: extrathyroidal extension; Anti-HCV: hepatitis C virus antibody; HBsAg: hepatitis B surface antigen; OR: odds ratio; CI: confidence interval.

Table 6. Stratified comparison of tumor aggressiveness features according to thyroid autoantibody status

Feature	Anti-TPO positive	Anti-TPO negative	OR (95% CI)†	p‡	Anti-Tg positive	Anti-Tg negative	OR (95% CI)†	p‡
Tumor size ≥ 1 cm	61/104 (58.7)	43/71 (60.6)	0.92 (0.50–1.71)	0.801 C	40/78 (51.3)	86/130 (66.2)	0.54 (0.30–0.96)	0.034 C
Pathological N1	8/104 (7.7)	4/71 (5.6)	1.40 (0.40–4.82)	0.764 F	6/78 (7.7)	9/130 (6.9)	1.12 (0.38–3.28)	0.836 C
Multifocality	57/104 (54.8)	41/71 (57.7)	0.89 (0.48–1.63)	0.701 C	49/78 (62.8)	68/130 (52.3)	1.54 (0.87–2.73)	0.139 C
Bilaterality	53/104 (51.0)	31/71 (43.7)	1.34 (0.73–2.46)	0.343 C	38/78 (48.7)	55/130 (42.3)	1.30 (0.74–2.28)	0.368 C
Capsular invasion	37/104 (35.6)	14/71 (19.7)	2.25 (1.11–4.57)	0.023 C	25/78 (32.1)	37/130 (28.5)	1.19 (0.64–2.18)	0.584 C
ETE	14/104 (13.5)	3/71 (4.2)	3.53 (0.97–12.76)	0.043 C	11/78 (14.1)	7/130 (5.4)	2.88 (1.07–7.79)	0.030 C
CLNM	10/104 (9.6)	5/71 (7.0)	1.40 (0.46–4.30)	0.550 C	9/78 (11.5)	8/130 (6.2)	1.99 (0.73–5.39)	0.170 C
LLNM	7/104 (6.7)	2/71 (2.8)	2.49 (0.50–12.35)	0.314 F	4/78 (5.1)	6/130 (4.6)	1.12 (0.31–4.09)	1.000 F

Data are expressed as n/valid N (%). Bold p-values indicate statistical significance ($p < 0.05$). Thyroid autoantibodies were measured in a subset of the cohort: anti-TPO in 175 of 521 patients (104 positive, 71 negative; 346 not tested) and anti-Tg in 208 of 521 patients (78 positive, 130 negative; 313 not tested). These analyses are therefore restricted to the tested subgroups and are exploratory. † Unadjusted odds ratio (antibody-positive vs. -negative). ‡ C: Pearson's chi-square test; F: Fisher's exact test (any expected count < 5). For the anti-TPO/ETE comparison the minimum expected count was 6.9, so chi-square applies ($p = 0.043$); Fisher's exact test as a sensitivity analysis gives $p = 0.066$. Abbreviations: CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; ETE: extrathyroidal extension; Anti-TPO: anti-thyroid peroxidase antibody; Anti-Tg: anti-thyroglobulin antibody; OR: odds ratio; CI: confidence interval.

Table 7. Multivariable binary logistic regression for the prediction of extrathyroidal extension (exploratory)

Variable	Adjusted OR†	95% CI	p
Age (per 1 year)	0.99	0.95–1.03	0.650
Male sex (vs. female)	0.96	0.27–3.41	0.952
Maximum tumor diameter (per 1 mm)‡	1.02	0.97–1.06	0.500
Anti-TPO positivity (vs. negative)	1.84	0.42–7.97	0.415
Anti-Tg positivity (vs. negative)	2.54	0.69–9.35	0.162

The model was fitted in the 147 patients (28.2% of the cohort) with complete data for all five covariates, among whom 14 ETE events were observed. Model fit: omnibus test $\chi^2 = 5.200$, $df = 5$, $p = 0.392$; $-2 \log$ likelihood = 87.260; Cox & Snell $R^2 = 0.035$; Nagelkerke $R^2 = 0.074$; overall classification accuracy 90.5%. Neither any individual covariate nor the model as a whole reached statistical significance. † In the SPSS model the last category of each categorical variable served as the reference; the estimates above have been re-expressed so that every comparison runs in the same direction as Tables 5 and 6. Model coefficients: anti-TPO-negative vs. positive $B = -0.609$ (SE 0.748); anti-Tg-negative vs. positive $B = -0.931$ (SE 0.665); female vs. male $B = 0.039$ (SE 0.645); age $B = -0.009$ (SE 0.020); tumor diameter $B = 0.015$ (SE 0.022); constant $B = -1.356$ (SE 1.297). ‡ Tumor diameter was modelled in millimetres, consistent with Table 2; expressed per centimetre the corresponding estimate is OR 1.16 (95% CI 0.75–1.80). With 14 events and five covariates the events-per-variable ratio is 2.8; the model is therefore prone to overfitting and is reported for transparency only. Abbreviations: OR: odds ratio; CI: confidence interval; ETE: extrathyroidal extension; Anti-TPO: anti-thyroid peroxidase antibody; Anti-Tg: anti-thyroglobulin antibody.

After adjusting for potential confounding factors—including age, sex, maximum tumor size, anti-TPO, and anti-Tg positivity—none of the variables remained statistically significant (all $p > 0.05$). Adjusted odds ratios were 1.84 (95% CI 0.42–7.97) for anti-TPO positivity and 2.54 (95% CI 0.69–9.35) for anti-Tg positivity.

The model was fitted in the 147 patients (28.2% of the cohort) with complete data for all five covariates, among whom 14 ETE events were observed; the events-per-variable ratio was therefore low (2.8), the model as a whole was not statistically significant (omnibus $\chi^2 = 5.20$, $df = 5$, $p = 0.392$; Nagelkerke $R^2 = 0.074$), and these

adjusted estimates should be interpreted as exploratory. This suggests that neither thyroid autoantibodies nor the evaluated demographic parameters were independent predictors of ETE in our cohort.

DISCUSSION

In the present study, we investigated the association between pre-operative HBV and HCV seropositivity and clinicopathological aggressiveness in a cohort of 521 patients with papillary thyroid carcinoma. To our knowledge, this is one of the few studies to evaluate both HBV and HCV serology, together with thyroid autoimmunity status, within a cohort restricted specifically to PTC rather than differentiated thyroid carcinoma as a whole. Overall, neither HBV nor HCV seropositivity was consistently associated with more aggressive tumor characteristics in our cohort, whereas younger age and thyroid autoantibody positivity appeared to be more closely linked to aggressive disease features.

The relationship between HBV infection and PTC has been examined in only a limited number of studies, with conflicting results. For instance, an analysis of 569 PTC patients demonstrated that HBsAg positivity was significantly associated with higher rates of bilaterality (36.9% vs. 25.2%) and central lymph node metastasis (71.4% vs. 60.0%). Furthermore, multivariate modeling within the same cohort identified HBsAg positivity as an independent predictor of central lymph node metastasis (adjusted OR, 1.80; 95% CI, 1.03–3.14) (4). In contrast, our study found no significant differences between HBsAg-positive and HBsAg-negative patients in multifocality, extrathyroidal extension, capsular invasion, lymphovascular or perineural invasion, or central/lateral lymph node metastasis; notably, bilaterality was significantly lower in the HBsAg-positive group (chi-square $p = 0.039$; sensitivity analysis with Fisher's exact test, $p = 0.072$), in contrast to the direction reported by Zhong et al. Furthermore, when patients with serological evidence of resolved HBV infection were compared to HBV-naïve patients, the only difference reached was a higher rate of capsular invasion in the resolved-infection group (30.0% vs. 11.0%; OR 3.46, 95% CI 1.14–10.45; $p = 0.033$), with no differences in any other histopathological aggressiveness indicator; with only 20 patients in

the resolved group this isolated result is most plausibly a chance finding among the many comparisons performed and requires confirmation. Our finding of lower bilaterality among HBsAg-positive patients contradicts previous reports; however, the very small size of our HBsAg-positive subgroup ($n = 12$) substantially limits the statistical power of this inference. It is highly probable that this isolated, borderline finding reflects a chance association arising from the limited sample size and the number of comparisons performed rather than a true biological effect. Furthermore, despite the small number of infected cases, the HBsAg seropositivity rate observed in our study cohort is consistent with regional epidemiological data, specifically supporting the findings of the TURHEP study, which reported an HBsAg seropositivity rate of 2.3% in the Aegean region (5). Beyond sample size constraints, the considerable inconsistency across studies in the literature may also reflect differences in the HBV markers examined, regional HBV endemicity, viral genotype distribution, and the specific clinical outcomes measured (e.g., overall risk of malignancy vs. within-tumor aggressiveness).

Data regarding HCV and thyroid carcinoma are similarly heterogeneous. A comprehensive meta-analysis of over 750,000 individuals initially showed no significant relationship between HCV infection and thyroid cancer risk (RR 2.09, 95% CI 0.78–5.64). However, this association reached statistical significance once a single highly heterogeneous study was excluded from the analysis (RR 2.86, 95% CI 1.63–5.03) (10). A subsequent meta-analysis by Wang et al. reported a markedly elevated risk of thyroid cancer among HCV-infected individuals (summary OR 16.36, 95% CI 4.65–57.62), alongside an increased risk of thyroid disease more broadly (summary OR 1.80) (12). In our cohort, however, Anti-HCV positivity was not associated with any of the clinicopathological aggressiveness parameters examined. This discrepancy likely stems, in part, from a fundamental difference in study design and research question: whereas most published meta-analyses address whether HCV infection increases the risk of developing thyroid carcinoma, our study evaluated whether HCV serostatus modifies tumor aggressiveness among patients already diagnosed with PTC — a distinct and less-studied question. In addition, the

extremely small number of Anti-HCV-positive patients in our cohort ($n = 4$), reflecting the low background HCV seroprevalence in Turkey (approximately 1%, per the TURHEP study) (5), severely limits statistical power and precludes any meaningful conclusion regarding a true absence of association.

Consistent with much of the existing literature, patients aged 55 years or younger in our cohort had significantly higher rates of central lymph node metastasis and overall N1 disease. This finding aligns with recent data from Duan et al., who, in a cohort of 540 PTC patients with coexisting Hashimoto's thyroiditis, identified age below 45 years as an independent risk factor for central lymph node metastasis (adjusted OR 2.95) (13). Similarly, Gao et al. reported that younger age was significantly associated with central lymph node metastasis in a univariate analysis among 296 PTC patients; however, this association lost its independent significance after adjusting for tumor size and other covariates (14). Regarding thyroid autoimmunity, positivity for both anti-TPO and anti-Tg was associated with extrathyroidal extension (ETE) in univariable analyses. Additionally, anti-TPO positivity was associated with higher capsular invasion rates. At first glance, these results appear to contradict the large meta-analysis by Tang et al. (15). They reported that Hashimoto's thyroiditis (HT) had a "protective" effect against ETE and lymph node metastasis, despite promoting multifocality and bilaterality. However, our findings align more closely with recent studies that evaluate TgAb and TPOAb independently, rather than treating HT as a single entity. For instance, Duan et al. (13) and Gao et al. (14) both demonstrated that TgAb positivity increases the risk of central lymph node metastasis. These data highlight that TgAb and TPOAb can exert highly divergent effects on tumor behavior within the same population. Notably, the direction of the anti-Tg associations was not uniform within our own data either: anti-Tg positivity was associated with a higher rate of ETE but with a lower proportion of tumors larger than 1 cm, a pattern partly compatible with the "protective" effect attributed to Hashimoto's thyroiditis and a further argument against treating "aggressiveness" as a single construct. However, it is critical to note that although univariable analyses linked these autoantibodies to extrathyroidal extension (ETE), this association

was no longer statistically significant in our multivariable model. Adjusting for covariates such as age and tumor size revealed that ETE is likely multifactorial rather than an independent consequence of a single autoantibody. Furthermore, our study defined autoimmunity solely by autoantibody seropositivity, rather than a definitive clinical or histological diagnosis of HT. This methodological difference likely captures an earlier or more heterogeneous autoimmune population, partly explaining why our findings diverge from the traditionally reported 'protective' pattern of HT. Finally, a notable limitation of our analysis is the concurrent anti-TPO and anti-Tg positivity in a subset of patients, which further complicates isolating Future studies could reconcile the two approaches by combining preoperative autoantibody titres with the systematic review of the thyroidectomy specimens for chronic lymphocytic thyroiditis, so that serologically and histologically defined autoimmunity can be analyzed both separately and in combination; this would clarify whether the divergent effects reported for TgAb and TPOAb reflect distinct biological processes or merely different stages of the same disease. the independent effect of each autoantibody.

Overall, our findings suggest that host- and immune-related factors—namely, younger age and thyroid autoimmunity—are more consistent predictors of tumor aggressiveness than chronic viral hepatitis. However, we cannot exclude a smaller, population-specific viral effect. Our study may have been underpowered to detect this due to the very low prevalence of active HBV (4.2%) and HCV (1.4%) infections, though these rates strongly align with national epidemiological data (5). Indeed, our sensitivity analysis indicated that only very large effects (minimum detectable OR ≥ 4.6 for HBsAg and ≥ 10 for anti-HCV comparisons) could have been detected with the available subgroup sizes.

This study has several notable strengths. First, it features a relatively large, histologically confirmed PTC-specific cohort, unlike prior studies that pooled multiple thyroid cancer histotypes. Second, our comprehensive HBV panel allowed us to statistically evaluate not only patients with active chronic HBV (HBsAg-positive) but also those with resolved infections and acquired immunity. Finally, the simultaneous assessment of both viral hepatitis markers and thyroid autoimmunity within

a single cohort addresses a significant gap in the current literature.

This study has several limitations. First, its retrospective, single-center design is inherently susceptible to selection bias. In particular, the lack of preoperative serological testing among approximately 45% of the cohort may have introduced systematic bias. This concern is substantiated by our own comparison of tested and untested patients (Supplementary Table S1): although the two groups were similar in age, sex and most tumor characteristics, patients without serology had significantly more lymphovascular invasion, extrathyroidal extension and nodal disease. The serologically characterized subgroup therefore under-represents the most aggressive tumors, which both limits the generalizability of the viral hepatitis analyses and further reduces their power to detect associations with aggressive histopathological features. Second, the very small number of infected patients (HBsAg-positive $n = 12$, Anti-HCV-positive $n = 4$) substantially limits statistical power and precluded the use of multivariate regression models specifically for the viral hepatitis subgroups. This increases the risk of Type II errors and spurious associations. Third, the absence of viral load (HBV DNA, HCV RNA) and genotype data precludes the evaluation of a relationship between viral replication and tumor aggressiveness. Fourth, thyroid autoantibody results were available in only a subset of patients (anti-TPO, 175/521; anti-Tg, 208/521), and antibody testing—like viral serology—may have been requested selectively, further limiting these exploratory analyses. Fifth, a large number of univariable comparisons were performed without adjustment for multiple testing, and some nominally significant findings may represent chance. Sixth, lymph node dissection was not performed systematically in all patients, so CLNM and LLNM rates partly reflect surgical selection rather than the true prevalence of nodal metastasis. Finally, the absence of longitudinal follow-up data precludes the evaluation of long-term outcomes such as recurrence, recurrence-free survival, and disease-specific survival; accordingly, our findings pertain exclusively to histopathological features at initial diagnosis and carry no direct prognostic implication. Seventh, the study period spans a change in the staging system, since the AJCC 8th edition took effect in January 2018; T-stage assignment may therefore

not be strictly uniform across the cohort, although the age threshold and the aggressiveness features analyzed here were applied consistently. Ultimately, we detected no association between background HBV or HCV seropositivity and histopathological aggressiveness in patients with PTC; given the small seropositive subgroups, this should not be construed as definitive evidence of no effect. While viral seropositivity showed no significant association, baseline factors such as younger age and underlying thyroid autoimmunity appeared to be more closely associated with aggressive tumor features. It is important to note, however, that the relatively low background rate of viral hepatitis in our region restricts the statistical strength of these viral findings. Moving forward, large-scale multicenter studies that track viral loads and long-term survival will be essential to fully understand whether these chronic viruses truly influence the prognosis of thyroid cancer.

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7-30.
2. Ringel MD, Sosa JA, Baloch Z, et al. 2025 American Thyroid Association Management Guidelines for Adult Patients with Differentiated Thyroid Cancer. *Thyroid.* 2025;35(8):841-985.
3. Hegedüs L, Wirth LJ, Tuttle RM. Management of Differentiated Thyroid Cancer. *N Engl J Med.* 2026;394(23):2340-2355.
4. Zhong Z, Yuan J, Chen X, et al. The Clinicopathological Features of Papillary

- Thyroid Carcinoma Patients with Positive Hepatitis B Surface Antigen. *Oncol Res Treat.* 2020;43(1-2):27-33.
5. Tozun N, Ozdogan O, Cakaloglu Y, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. *Clin Microbiol Infect.* 2015;21(11):1020-1026.
 6. Punzalan CS, Bukong TN, Szabo G. Alcoholic hepatitis and HCV interactions in the modulation of liver disease. *J Viral Hepat.* 2015;22(10):769-776.
 7. Fallahi P, Ferrari SM, Politti U, Giuggioli D, Ferri C, Antonelli A. Autoimmune and neoplastic thyroid diseases associated with hepatitis C chronic infection. *Int J Endocrinol.* 2014;2014:935131.
 8. Kamiza AB, Su FH, Wang WC, Sung FC, Chang SN, Yeh CC. Chronic hepatitis infection is associated with extrahepatic cancer development: a nationwide population-based study in Taiwan. *BMC Cancer.* 2016;16(1):861.
 9. Wu YK, Jiang TT, Su YH, et al. The Potential Role of Virus Infection in the Progression of Thyroid Cancer. *World J Oncol.* 2024;15(3):382-393.
 10. Wang P, Jing Z, Liu C, et al. Hepatitis C virus infection and risk of thyroid cancer: A systematic review and meta-analysis. *Arab J Gastroenterol.* 2017;18(1):1-5.
 11. Archin Dialameh P, Saki F, Monabbati A, Dehghanian A, Valibeigi B, Soveid M. Detection of Human Papillomavirus in Papillary Thyroid Carcinoma and its Association with Tumor Staging and Pathologic Features. *Iran J Med Sci.* 2021;46(4):256-262.
 12. Wang H, Liu Y, Zhao Y. The association of hepatitis C virus infection and thyroid disease: A systematic review and meta-analysis. *Int J Biol Markers.* 2021;36(4):3-9.
 13. Duan C, Yu P, Wei X, et al. The role of age and antibodies in central regional lymph node metastases of papillary thyroid carcinoma combined with hashimoto's thyroiditis. *BMC Cancer.* 2026;26(1):896.
 14. Gao X, Luo W, He L, Cheng J, Yang L. Predictors and a Prediction Model for Central Cervical Lymph Node Metastasis in Papillary Thyroid Carcinoma (cN0). *Front Endocrinol (Lausanne).* 2022;12:789310.
 15. Tang Q, Pan W, Peng L. Association between Hashimoto thyroiditis and clinical outcomes of papillary thyroid carcinoma: A meta-analysis. *PLoS One.* 2022;17(6):e0269995.

Supplementary Table S1. Baseline and histopathological characteristics of patients with and without preoperative HBV serology

Characteristic	Serology available (n = 289)	Serology not available (n = 232)	p
Age (years), mean $\pm$ SD	56.3 $\pm$ 14.0	57.7 $\pm$ 14.7	0.260*
Age $\leq$ 55 years	121/289 (41.9)	101/232 (43.5)	0.702
Sex, female	210/289 (72.7)	171/232 (73.7)	0.790
Tumor size > 1 cm	182/289 (63.0)	132/232 (56.9)	0.159
Multifocality	150/289 (51.9)	100/227 (44.1)	0.077
Bilaterality	132/289 (45.7)	89/228 (39.0)	0.130
Capsular invasion	68/287 (23.7)	56/225 (24.9)	0.754
Lymphovascular invasion	13/289 (4.5)	31/228 (13.6)	<0.001
Extrathyroidal extension	13/289 (4.5)	27/227 (11.9)	0.002
CLNM	24/289 (8.3)	26/228 (11.4)	0.237
LLNM	18/289 (6.2)	21/228 (9.2)	0.202
Pathological N1	21/289 (7.3)	29/230 (12.6)	0.040
M1 at diagnosis	3/289 (1.0)	5/230 (2.2)	0.476

Data are expressed as n/valid N (%) unless otherwise indicated; denominators differ between rows because of variable-specific missing data. Bold p-values indicate statistical significance ($p < 0.05$). Groups are defined by the availability of preoperative HBsAg testing. * Mann–Whitney U test (age was not normally distributed; Shapiro–Wilk $p < 0.01$ in both groups). All other comparisons used Pearson's chi-square test, except M1 status, for which Fisher's exact test was applied. Patients without preoperative serology had significantly higher rates of lymphovascular invasion, extrathyroidal extension and pathological N1 disease; age, sex, tumor size, multifocality, bilaterality, capsular invasion, CLNM, LLNM and M1 status did not differ significantly. This is addressed in the Limitations. Abbreviations: SD: standard deviation; CLNM: central lymph node metastasis; LLNM: lateral lymph node metastasis; HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen.