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ORIGINAL RESEARCH

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Worse survival and higher rates of relapse in U.S. Armenians with papillary thyroid cancer

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Abstract

Objectives: Papillary thyroid cancer (PTC) is the most frequent subtype of thyroid cancer with overall favorable survival. Currently, little is known about the PTC experience within the United States (U.S.) Armenians. We performed the first study comparing clinicopathologic variables and clinical outcomes of U.S. Armenian PTC patients to a matched control group of non-Armenians.

Methods: We performed a single-center, retrospective, case–control study of adult Armenian PTC patients who received care at COH from 2005 to 2022. Armenian ethnicity was determined by surnames ending in "-ian" and "-yan". We report and compare clinicopathologic presentation and disease outcomes with a gender- and age-matched control non-Armenian population.

Results: Fifty-eight Armenian patients comprised our study cohort. Positive margin status ($p = .038$), angioinvasion ($p = .006$), and extrathyroidal extension ($p = .014$) were more prevalent in the Armenian population. Higher rates of both persistent disease and death due to disease were seen in the Armenians regardless of age groupings. Multivariable analysis revealed significant impact of Armenian status on outcomes. Calculated 5- and 10- year disease-specific survival rates in the Armenian cohort were 88% and 73.2%, respectively, compared with 100% and 94.6% in the non-Armenian group ($p < .002$). The 5- and 10- year progression-free survival was worse in the Armenian group at 61.8% and 50.1%, respectively, compared with 87.5% and 87.5% in the non-Armenian group ($p < .001$).

Conclusion: Armenian PTC patients displayed more aggressive disease than non-Armenians. In addition, Armenian PTC patients had higher incidence of disease relapse and worse clinical outcomes.

Level of Evidence: 5

KEYWORDS
Armenian, disease progression, papillary thyroid cancer, recurrence, survival

1 | INTRODUCTION

PTC is the most frequent subtype of thyroid cancer accounting for about 85% of all thyroid cancer cases with an overall favorable 10-year survival of 97%, and 20-year survival of 90%.[1,2] With the abundance of research supporting excellent prognosis, the American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) have advocated for less aggressive management of thyroid cancer with considerations of lobectomy, less radioactive iodine (RAI) ablation, and active surveillance for small and histologically favorable thyroid cancer.[3,4]

Despite most PTC being indolent, a subset behaves aggressively despite best treatment. Many studies have identified unfavorable features that impact PTC survival including aggressive histopathologic variants, size >4 cm, older age ≥55 years, multifocality, extrathyroidal extension, lymphovascular invasion, and the presence of BRAF V600E and/or TERT mutations.[2,5–10] Moreover, aggressive PTC variants have been shown to have increased risk of RAI refractory disease, higher propensity for recurrence, distant metastasis, and mortality compared to classical PTC.[3] The ATA risk stratification system for differentiated thyroid cancer is widely used to stratify prognosis and guide therapeutic strategies.[3]

It has been difficult to ascertain if patient ethnicity independently impacts thyroid cancer outcomes. Many studies have suggested that thyroid cancer in Filipinos is more advanced at diagnosis and associated with higher risk of recurrence and cancer-related mortality.[11–14] Despite convincing evidence that Filipino ethnicity negatively impacts thyroid cancer outcomes, to date, no clinical guideline includes ethnicity as a prognostic factor to guide clinical decision making and management.

In 2021, there were 454,884 Armenians in the United States (U.S.) with 194,773 (43%) living in Los Angeles County.[15] This single area holds the largest Armenian population in the U.S., and in the world outside Armenia. Despite the large concentration of U.S. Armenians, there is a paucity of cancer studies looking at this ethnic group. The current published studies on thyroid cancer in Los Angeles County do not specifically isolate the Armenian cohort from the non-Hispanic White population.[11,16,17] City of Hope (COH) is a National Cancer Institute designated comprehensive cancer center within Los Angeles County and serves as a major destination for cancer care for the Armenian population based on its proximity to major Armenian suburban populations. Over a 20-year single-center experience, we anecdotally noticed Armenians presenting with more challenging disease. As such, we aimed to objectively look at our U.S. Armenian patients with thyroid cancer and compare their clinicopathologic presentation and disease outcomes with gender- and age-matched non-Armenians treated by the same multidisciplinary team. Other secondary outcomes included looking at progression-free survival (PFS) and disease-specific survival (DSS). We chose to focus on PTC as it is the most common histopathology of thyroid cancer which allows for a uniform basis for comparison. To the best of our knowledge, this is the first study to report on clinicopathologic variables and clinical outcomes relevant to PTC in the U.S. Armenian population.

2 | METHODS

2.1 | Study population

We performed a single-center, retrospective, case–control study of adult Armenian PTC patients who received care at COH from January 1, 2005 to November 1, 2022. A total of 1479 PTC patients were retrieved from the COH cancer registry population by our research informatics team. Cases were defined as Armenian patients (age 18 or older) who were diagnosed with PTC through cytopathology or surgical pathology reports. Armenian ethnicity was determined by surnames ending in "-ian" and "-yan" which has been known to be a reliable identifier of Armenian descent.[18] Exclusion criteria included those with missing initial thyroidectomy slides for review by our treatment at COH and those we were unable to confirm Armenian ethnic background. These strict criteria further narrowed our cohort to 58 cases. Upon discussion with our biostatistician, controls were non-Armenian PTC patients who were age- and sex-matched 1:1 with our cases and had similar follow-up time compared to cases and were treated in the same time frame as the matched cases. Details of this process is outlined in Figure 1.

To ensure accuracy and consistency, all data was collected manually and verified by our team. This study was approved by the COH Institutional Review Board (IRB #17137).

2.2 | Statistical analyses

Continuous variables were analyzed using Wilcoxon rank-sum test and categorical variables were analyzed by Fisher's exact test. The Kaplan–Meier method with the log-rank test of significance was applied to compare Armenians to non-Armenians for DSS and PFS. Multivariable analysis included a logistic regression to determine variables associated with group status (non-Armenian versus Armenian), and Cox proportional hazards models for 17-year DSS, and PFS. Follow-up to 17 years was chosen as this represents the longest time available. Analyses were performed using Stata MP version 14.2 (StataCorp, College Station, TX).

3 | RESULTS

3.1 | Study population and baseline characteristics

A total of 58 patients met inclusion criteria in our Armenian study cohort and therefore 58 patients constituted the matched non-Armenian control group. Patient characteristics and disease outcomes are shown in Table 1. The Armenian group consisted of mostly middle-aged females ($n = 38$, 65.5%) with median age at diagnosis of 57.5 years (interquartile range [IQR] 45–70). Additionally, there were no significant differences in PTC stage or histologic variants between the two groups with most cases being PTC stage 1 (69.0% vs. 77.6%, $p = .485$) and classical variant (79.3% vs. 81%, $p = .801$). The

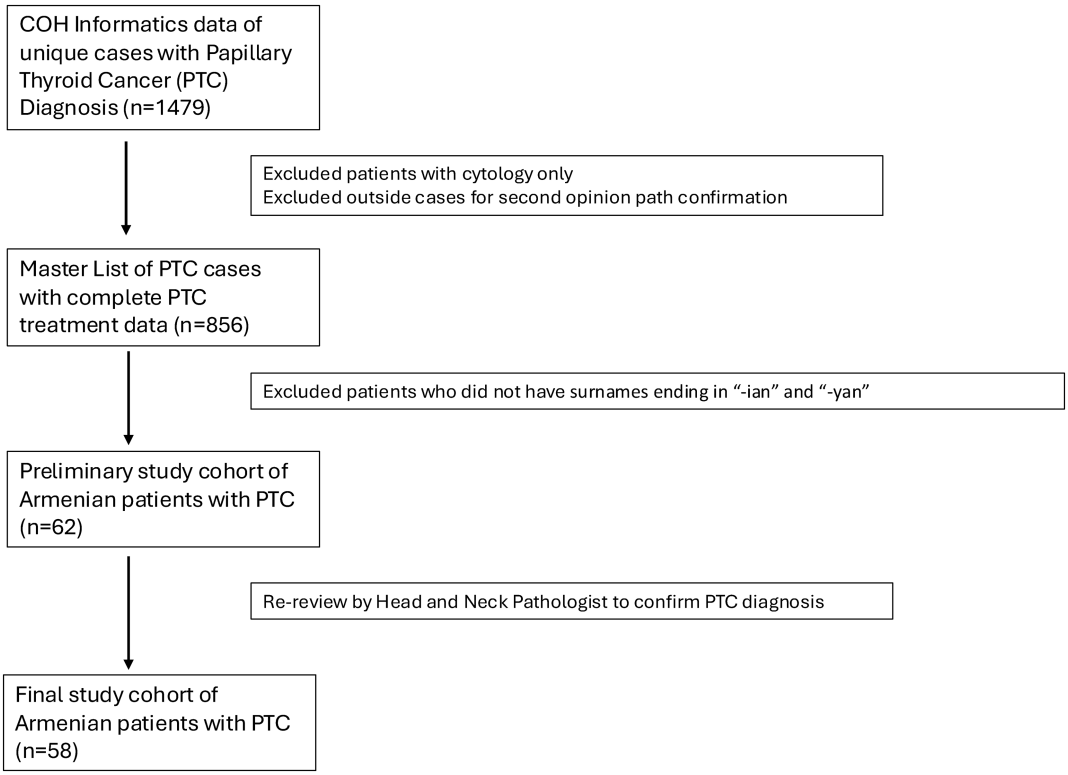

FIGURE 1 Flowchart of patient case cohort selection and control matching.

Armenians compared to non-Armenians had significantly worse disease outcomes at last follow up with significantly more Armenians with death from disease ($n = 10$, 17.2% vs. $n = 1$, 1.7%, $p = .008$), locoregional recurrence ($n = 20$, 34.5% vs. $n = 5$, 8.6%, $p = .001$), and distant disease recurrence ($n = 11$, 19% vs. $n = 2$, 3.5%, $p = .016$) during a similar mean follow-up time of 75 months in the Armenian group and 86 months in the non-Armenian group, $p = .271$.

Table 2 further stratifies patient characteristics and outcomes based on American Joint Committee on Cancer (AJCC) 8th edition age grouping (<55 and ≥55 years of age). This age stratification allowed for data analysis based on the AJCC 8th edition staging for PTC. All younger Armenians had stage 1 PTC while the older Armenian group had a mixed distribution of disease stage but mostly stage II ($n = 14$, 56.0%) at presentation. Higher rates of disease recurrence were seen in both the younger and older Armenian cohorts. Comparisons between the younger patient cohorts revealed significantly higher rates of locoregional recurrence in the Armenian group ($n = 9$, 27.3% vs. $n = 1$, 3.1%, $p = .013$). Although comparisons of distant disease relapse in the young Armenian cohort did not reach statistical significance, all cases of distant recurrence in young patients were in the Armenian cohort ($n = 3$, 9.1%, $p = .238$). Comparisons between the older patient cohorts revealed higher rates of both locoregional and distant relapse in the Armenians approaching statistical significance ($n = 11$, 44.0% vs. $n = 4$, 16.0%, $p = .062$ and $n = 8$, 32.0% vs. $n = 2$, 8.0%, $p = .074$, for locoregional and distant recurrence, respectively). Significantly higher rates of both persistent disease at the last follow-up (AWD) and death due to disease (DOD) were also seen in the Armenians regardless of age groupings ($p = .001$ and $p = .027$ in younger and older cohorts, respectively). A closer look reveals no evidence of persistent disease in the young non-Armenian patients, whereas approximately 25% of the young Armenian patients had persistent disease at last follow-up. Three young Armenians and 7 older Armenians died of disease (9.1% and 28.0%, respectively). There were no cancer-related deaths in the young non-Armenian cohort and only 1 cancer related death in the older non-Armenian cohort.

Table 3 outlines the histopathologic differences of the primary thyroid cancers between the two groups independent of AJCC 8th ed. age categories for cancer staging. Significantly higher rates of positive surgical margin ($n = 21$, 36.2% vs. $n = 11$, 19.0%, $p = .038$), angioinvasion ($n = 8$, 13.8% vs. $n = 0$, 0.0%, $p = .006$), and extrathyroidal extension ($n = 23$, 39.7% vs. $n = 11$, 19.0%, $p = .014$) were seen in the Armenian cohort. Tumor size, focality, and lymphatic invasion were not significant differentiators between study and control cohorts. Table 4 presents the same data stratified by AJCC 8th ed. age-based staging. Positive margins, angioinvasion, and extrathyroidal extension were more frequently encountered in both the young and old Armenian cohorts.

Table 5 shows pathologic differences of regional nodes between the two groups independent of AJCC 8th ed. age categories for cancer staging. No differences were seen in terms of lymph node involvement, number of lymph nodes examined, number of positive lymph nodes, largest positive lymph node, and presence or absence of extranodal extension in both study and control cohorts. The Armenian

TABLE 1 Patient characteristics and disease outcomes.

	Armenian ($n = 58$)	Non-Armenian ($n = 58$)	p value*
Age, *n* (%)			
<55	33 (56.8)	33 (56.8)	1.000
≥55	25 (43.1)	25 (43.1)	
Sex, *n* (%)			
Female	38 (65.5)	38 (65.5)	1.000
Male	20 (34.5)	20 (34.5)	
Stage			
Stage I	40 (69.0)	45 (77.6)	.485
Stage II	14 (24.1)	12 (20.7)	
Stage III	3 (5.2)	1 (1.7)	
Stage IV	1 (1.7)	0 (0)	
Histologic variants			
Classical variant	46 (79.3)	47 (81.0)	.801
Follicular variant	10 (17.5)	9 (15.5)	
Tall cell variant	1 (1.7)	1 (1.7)	
Insular variant	1 (1.7)	0 (0)	
Oncocytic variant	0 (0)	1 (1.7)	
Disease status, *n* (%)			
AWOD	35 (60.3)	53 (91.4)	**<.001**
AWD	9 (15.2)	1 (1.7)	
DOD	10 (17.2)	1 (1.7)	
DOC	2 (3.5)	2 (3.5)	
Unknown	2 (3.5)	1 (1.7)	
Vital status, *n* (%)			
Alive	46 (79.3)	55 (94.8)	**.013**
Dead	12 (20.7)	3 (5.2)	
Death by PTC, *n* (%)			
No	48 (82.8)	57 (98.3)	**.008**
Yes	10 (17.2)	1 (1.7)	
Recurrence, any site, *n* (%)			
No	37 (63.8)	52 (89.7)	**.001**
Yes	21 (36.2)	6 (10.3)	
Locoregional recurrence, *n* (%)			
No	38 (65.5)	53 (91.4)	**.001**
Yes	20 (34.5)	5 (8.6)	
Distant disease recurrence, *n* (%)			
No	47 (81.0)	56 (96.5)	**.016**
Yes	11 (19.0)	2 (3.5)	
Follow-up time months, mean (SD)	75.1 (51.1)	86.3 (57.9)	.271

Abbreviations: AJCC, American Joint Committee on Cancer; AWOD, alive without disease; AWD, alive with disease; DOC; dead of other cause; DOD, dead of disease.

*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data. Bold indicates p value < 0.05.

cohorts had larger sized nodes across group comparisons. Although lymph node size did not meet statistical significance for the overall group comparisons (mean 1.8 cm vs. 0.98 cm, $p = .059$), it reached significance when comparing older Armenian to older non-Armenian cohorts (mean 2.4 cm vs. 1.0 cm, $p = .043$) as depicted in Table 6. Table 6 presents the characteristics of regional nodes stratified by AJCC 8th ed. age-based staging.

Aspects of multidisciplinary clinical management are captured in Table 7 and reveal no differences in management across Armenian and non-Armenian cohorts in terms of surgery type, initial neck dissection, cumulative RAI exposure, and use of systemic therapies. However, twice as many Armenians were treated with larger RAI dosage >150 mCi ($n = 14$, 32.7% vs. $n = 7$, 16.7%, $p = .089$) and/or systemic therapy ($n = 8$, 13.8% vs. $n = 4$, 6.9%, $p = .223$). Table 8 presents the same data stratified by AJCC 8th ed. age-based staging. Of note, a higher percentage of young Armenian patients received larger RAI dosage >150 mCi ($n = 9$, 37.5% vs. $n = 3$, 12.5%, $p = .093$) and/or systemic therapy ($n = 4$, 12.2% vs. $n = 0$, 0%, $p = .114$).

Multivariable analysis was performed to determine factors predicting group membership. Non-Armenian versus Armenian status was the dependent variable in a multivariable logistic regression with backward stepwise entry. Stepwise criteria required a p value of .20 to remain in the model. Backward entry included all predictors in the initial model and then removed those that failed to meet the p value criterion. The initial model included age, sex, stage, extrathyroidal extension, angioinvasion, lymphatic invasion, disease focality, margins, extranodal extension, positive lymph nodes (no/yes), procedure (partial vs. total), neck dissection (no/yes), receipt of RAI (no/yes), and receipt of any systemic therapy (no/yes). As there was only one case with stage IV disease, this case was dropped from multivariable analyses. Only age and margins remained in the model (Table 9) with the odds ratio for margins at the cusp of significance (OR 2.37, 95% CI 1.00–5.64, $p = .050$). Positive margin cases were twice as likely to be Armenian.

To model DSS at 17 years or PFS, a Cox proportional hazards model with backward stepwise entry was created. As before, a p value of .20 was required to remain in the model. For DSS, age, extrathyroidal extension, and group remained in the model (Table 10). While extrathyroidal extension was in the final model, the hazard ratio of 8.11 was on the cusp of significance (95% CI 0.95–69.29, $p = .056$). Group status was significant with a hazard ratio for Armenian status of 8.19 (95% CI 1.06–63.00, $p = .043$) indicating that Armenians had an eight times greater disease-specific mortality risk compared with non-Armenians, controlling for age and extrathyroidal extension.

For PFS, sex, stage, systemic therapy, and group remained as significant predictors in the final model (Table 11). In this model, Armenian status had a hazard ratio of 3.90 (95% CI 1.52–10.01, $p = .005$), indicating a near 4 times greater risk of recurrence for Armenians compared with non-Armenians, controlling for sex, stage, and receipt of systemic therapy.

TABLE 2 Patient clinical characteristics by younger (<55 years) versus older (≥55 years) age group.

	Younger Armenian ($n = 33$)	Younger non-Armenian ($n = 33$)	p value*	Older Armenian ($n = 25$)	Older non-Armenian ($n = 25$)	p value*
Sex, *n* (%)						
Female	22 (66.7)	25 (75.8)	.587	16 (64.0)	13 (52.0)	.567
Male	11 (33.3)	8 (24.2)		9 (36.0)	12 (48.0)	
AJCC 8th Ed. stage at presentation, *n* (%)						
I	33 (100)	33 (100)	1.000	7 (28.0)	12 (48.0)	.311
II	—	—		14 (56.0)	12 (48.0)	
III	—	—		3 (12.0)	1 (4.0)	
IV	—	—		1 (4.0)	0 (0)	
Disease status, *n* (%)						
AWOD	23 (69.7)	33 (100)	**.001**	12 (44.0)	20 (80.0)	**.027**
AWD	5 (15.1)	0 (0)		4 (20.0)	1 (4.0)	
DOD	3 (9.1)	0 (0)		7 (28.0)	1 (4.0)	
DOC	0 (0)	0 (0)		2 (8.0)	2 (8.0)	
Unknown	2 (6.1)	0 (0)		0 (0)	1 (4.0)	
Vital status, *n* (%)						
Alive	30 (90.9)	33 (100)	.238	16 (64.0)	22 (88)	.095
Dead	3 (10.0)	0 (0)		9 (36.0)	3 (12)	
Death by PTC, *n* (%)						
No	30 (90.9)	33 (100)	.238	18 (72.0)	24 (96.0)	**.049**
Yes	3 (10.0)	0 (0)		7 (28.0)	1 (4.0)	
Recurrence, any site, *n* (%)						
No	24 (72.7)	32 (96.9)	**.013**	13 (52.0)	20 (80.0)	.072
Yes	9 (27.3)	1 (3.1)		12 (48.0)	5 (20.0)	
Locoregional disease recurrence, *n* (%)						
No	24 (72.7)	32 (96.6)	**.013**	14 (56.0)	21 (84.0)	.062
Yes	9 (27.3)	1 (3.1)		11 (44.0)	4 (16.0)	
Distant disease recurrence, *n* (%)						
No	30 (90.9)	33 (100)	.238	17 (68.0)	23 (92.0)	.074
Yes	3 (9.1)	0 (0)		8 (32.0)	2 (8.0)	
Follow-up time months, mean (SD)	74.6 (47.3)	89.0 (54.4)	.412	75.7 (56.6)	82.7 (55.3)	.560

Abbreviations: AJCC, American Joint Committee on Cancer; AWOD, alive without disease; AWD, alive with disease; DOC; dead of other cause; DOD, dead of disease.
*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data. Bold indicates p value < 0.05.

Figure 2 shows the Kaplan–Meier curves for DSS. The 5- and 10-year DSS rates were significantly lower for the Armenian cohort at 88% and 73.2%, respectively, compared to 100% and 94.6% for the non-Armenian group ($p < .002$). Figure 3 shows the Kaplan–Meier curves for PFS. Similarly, the 5- and 10-year PFS were worse in the Armenian cohort at 61.8% and 50.1%, respectively, compared with 87.5% and 87.5% for the non-Armenian group ($p < .001$).

4 | DISCUSSION

COH's prime location being in the heart of Los Angeles County and a large treatment referral center for thyroid cancer lends itself to a large U.S. Armenian thyroid cancer subpopulation. We are the first to perform a study looking at the U.S. Armenian patient population in terms of histopathologic characteristics, clinical outcomes, and survivorship. Prior studies evaluating the effect of race and PTC are limited because they do not separate Armenians from the White cohort.[11,16,17] One large retrospective study published in 2023 demonstrated improved but persistent thyroid cancer care disparities in racial minorities as compared to Whites since the release of the 2015 ATA guidelines.[17] Our study, however, suggests that within the non-Hispanic White cohort with thyroid cancer, there may be significant nuances in different ethnic subgroups.

We found that PTC affected more Armenian women than men supporting a prior study that found thyroid cancer to be three times

TABLE 3 Pathology characteristics of primary tumor.

	Armenian ($n = 58$)	Non-Armenian ($n = 58$)	p value*
Tumor size, *n* (%)			
<1 cm	11 (19.0)	13 (22.4)	.448
1–2 cm	21 (36.2)	26 (44.8)	
>2–4 cm	17 (29.3)	15 (25.9)	
>4 cm	9 (15.5)	4 (7.0)	
Multifocal disease, *n* (%)			
Unifocal	29 (50.0)	30 (51.7)	.853
Multifocal	29 (50.0)	28 (48.3)	
Lymphatic invasion, *n* (%)			
No	31 (53.5)	30 (51.7)	.852
Yes	27 (46.6)	28 (48.3)	
Angioinvasion			
No	50 (86.2)	58 (100)	**.006**
Yes	8 (13.8)	0 (0)	
Extrathyroidal extension			
No	35 (60.3)	47 (81.0)	**.014**
Yes	23 (39.7)	11 (19.0)	
Margin status			
Negative	37 (63.8)	47 (81.0)	**.038**
Positive	21 (36.2)	11 (19.0)	

*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data. Bold indicates p value < 0.05.

more common in Armenian women than in men in almost all age groups.[19] Positive surgical margin, angioinvasion, extrathyroidal extension, and both locoregional and distant relapse of disease were more common in the Armenian cohort. Armenians had more significant disease progression and disease-related mortality regardless of age groupings; there were more patients living with disease or dead of disease compared with non-Armenians. In fact, this generally indolent disease proved fatal in nearly 10% of our young Armenian patient population. Although our single institution study revealed PTC to be harder to control in the Armenian patients, statistical significance was missed for some comparisons due to small sample size. Larger population studies are needed to validate our findings.

Overall, 5- and 10-year recurrence rates in the Armenian group was grim as compared to the general US population with 38.2% vs. 5.7% relapse rates at 5-years and 49.9% vs. 9.4% relapse rates at 10-years, respectively.[20] Our Armenian population had a 10-year DSS rate of 73.2% which was lower than that previously reported (97.1% for lobectomy and 97%–98.4% for total thyroidectomy) in the general U.S. population.[20] Our findings are concordant with prior publication by Khachatrian et al. who found higher mortality in Armenians with regional and distant metastases.[19,21]

Potential contributing factors to observed worse thyroid cancer outcomes may be owed to healthcare inequities and disparities in diagnosis and treatment. These include socioeconomical hardships, lack of health education, limited English fluency or technology savviness compromising communications, differences in fundamental cultural perceptions and behavior regarding cancer diagnosis and

TABLE 4 Pathology characteristics of primary tumor by younger (<55 years) versus older (≥55 years) age group.

	younger armenian ($n = 33$)	younger non-armenian ($n = 33$)	p value*	Older Armenian ($n = 25$)	Older non-Armenian ($n = 25$)	p value*
Tumor size, *n* (%)						
<1 cm	4 (12.1)	6 (18.2)	.222	7 (28.0)	7 (28.0)	.924
1–2 cm	16 (39.4)	19 (57.6)		5 (20.0)	7 (28.0)	
>2–4 cm	9 (33.3)	8 (24.2)		8 (32.0)	7 (28.0)	
>4 cm	4 (15.2)	0 (0.0)		5 (20.0)	4 (16.0)	
Multifocal disease, *n* (%)						
Unifocal	16 (48.5)	15 (45.4)	1.000	13 (52.0)	15 (60.0)	.776
Multifocal	17 (51.5)	18 (54.6)		12 (48.)	10 (40.0)	
Lymphatic invasion, *n* (%)						
No	19 (57.6)	16 (48.5)	.622	12 (48.0)	14 (56.0)	.778
Yes	14 (42.4)	17 (51.5)		13 (52.0)	11 (44.0)	
Angioinvasion						
No	28 (84.8)	33 (100)	.053	22 (88.0)	25 (100)	.235
Yes	5 (15.2)	0 (0)		3 (12.0)	0 (0)	
Extrathyroidal extension						
No	23 (69.7)	29 (87.9)	.130	12 (48.0)	18 (72.0)	0.148
Yes	10 (30.3)	4 (12.1)		13 (52.0)	7 (28.0)	
Margin status						
Negative	23 (69.7)	28 (84.8)	.240	14 (56.0)	19 (76.0)	.232
Positive	10 (30.3)	5 (15.2)		11 (44.0)	6 (24.0)	

*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data.

TABLE 5 Pathology characteristics of regional nodes.

	Armenian ($n = 58$)	Non-Armenian ($n = 58$)	p value*
Lymph node involvement, *n* (%)			
No	32 (55.2)	30 (51.7)	.710
Yes	26 (44.8)	28 (48.3)	
Number of lymph nodes examined, mean (SD)	22.6 (29.5)	13.8 (17.3)	.085
Number of positive lymph nodes, mean (SD)	5.6 (4.0)	6.3 (8.3)	.688
Largest positive lymph node size in cm, mean (SD)	1.8 (1.5)	0.98 (0.9)	.059
Extranodal extension, *n* (%)			
No	47 (81.0)	49 (84.0)	.623
Yes	11 (19.0)	9 (15.5)	

*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data.

outlook, limited access to high-volume surgeons and evidence-based guideline-directed management.[22] Furthermore, racial/ethnic minority subgroups have limited enrollment into clinical trials for systemic therapies for thyroid cancer.[23] Strategies are needed to identify such barriers and mitigate impact on thyroid cancer outcomes. There is a need for increased awareness of health disparities and cross-cultural education for providers, so they are better attuned to patients' values, beliefs, and behaviors and, ultimately, more effective in gaining trust and compliance in treatment recommendations and subsequent follow-up.[24]

Other potential contributing factor for worse outcomes in Armenian PTC patients may be biologic and inherent in the genetic and/or epigenetic makeup of the tumor and tumor microenvironment. Unfortunately, we were unable to draw meaningful tumor genetic comparisons between the groups, as sufficient data for comparisons were lacking at the time of this analysis. Potential future studies could examine genomic sequencing of the cohorts to allow such

TABLE 6 Pathology characteristics of regional nodes by younger (<55 years) versus older (≥55 years) age group.

	Younger Armenian ($n = 33$)	Younger non-Armenian ($n = 33$)	p value*	Older Armenian ($n = 25$)	Older non-Armenian ($n = 25$)	p value*
Lymph node involvement, *n* (%)						
No	19 (57.6)	16 (48.5)	.622	13 (52.0)	14 (56.0)	1.000
Yes	14 (42.4)	17 (51.5)		12 (48.0)	11 (44.0)	
Number of lymph nodes examined, mean (SD)	17.7 (5.0)	14.8 (3.4)	.638	29.3 (7.8)	12.2 (3.2)	.055
Number of positive lymph nodes, mean (SD)	4.8 (0.9)	5.9 (1.8)	.577	6.6 (1.3)	6.4 (2.7)	.956
Largest positive lymph node size in cm, mean (SD)	1.3 (1.3)	0.8 (0.9)	.376	2.4 (1.7)	1.0 (0.9)	**.043**
Extranodal extension, *n* (%)						
No	29 (87.9)	28 (84.8)	1.000	18 (72.0)	21 (84.0)	.496
Yes	4 (12.1)	5 (15.2)		7 (28.0)	4 (16.0)	

*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data. Bold indicates p value < 0.05.

TABLE 7 Clinical management.

	Armenian ($n = 58$)	Non-Armenian ($n = 58$)	p value*
Surgery type, *n* (%)			
Partial	9 (15.5)	7 (12.1)	.590
Total	49 (84.5)	51 (87.3)	
Initial neck dissection, *n* (%)			
None	16 (27.6)	12 (20.7)	.240
Central	27 (46.6)	36 (62.1)	
Central & lateral	15 (25.9)	10 (17.3)	
Cumulative RAI, *n* (%)			
None	15 (25.9)	16 (27.6)	.233
≤150 mCi	29 (50.0)	35 (60.3)	
>150 mCI	14 (24.1)	7 (12.1)	
Systemic therapy, *n* (%)			
No	50 (86.2)	54 (93.1)	.223
Yes	8 (13.8)	4 (6.9)	

Abbreviation: mCi, millicuries.
*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data.

TABLE 8 Clinical management by younger (<55 years) versus older (≥55 years) age group.

	Younger Armenian ($n = 33$)	Younger non-Armenian ($n = 33$)	p value*	Older Armenian ($n = 25$)	Older non-Armenian ($n = 25$)	p value*
Surgery type, *n* (%)						
Partial	7 (21.2)	2 (6.1)	.149	2 (8.0)	5 (20.0)	.417
Total	26 (78.8)	31 (93.9)		23 (92.0)	20 (80.0)	
Initial neck dissection, *n* (%)						
None	8 (24.2)	4 (12.1)	.417	8 (32.0)	8 (32.0)	.368
Central	18 (54.6)	23 (69.7)		9 (36.0)	13 (52.0)	
Central & lateral	7 (21.2)	6 (18.2)		8 (32.0)	4 (16.0)	
Cumulative RAI, *n* (%)						
None	9 (27.3)	9 (27.3)	.136	6 (24.0)	7 (28.0)	1.000
≤150 mCi	15 (45.5)	21 (63.6)		14 (56.0)	14 (56.0)	
>150 mCI	9 (27.3)	3 (9.10)		5 (20.0)	4 (16.0)	
Systemic therapy, *n* (%)						
No	29 (87.8)	33 (100)	.114	21 (84.0)	21 (84.0)	1.000
Yes	4 (12.2)	0 (0)		4 (16.0)	4 (16.0)	

Abbreviation: mCi, millicuries.
*p value estimated from Student's t-test for continuous data and Fisher's exact test for categorical data.

TABLE 9 Logistic regression of group by predictor.

Variables	OR (95% CI)	p value
Age	0.99 (0.97–1.02)	.651
Margins		
Negative (reference)	1.00	
Positive	2.37 (1.00–5.64)	**.050**

Note: Bold indicates p value < 0.05.

TABLE 10 Cox proportional hazard model for disease-specific survival.

Variables	HR (95% CI)	p value
Age	1.06 (1.01–1.11)	**.018**
Extrathyroidal extension		
No (reference)		
Yes	8.11 (0.95–69.29)	.056
Group		
Non-Armenian (reference)		
Armenian	8.19 (1.06–63.00)	**.043**

Note: Bold indicates p value < 0.05.

TABLE 11 Cox proportional hazard model for progression-free survival.

Variables	HR (95% CI)	p value
Sex		
Male (reference)	1.00	
Female	0.38 (0.17–0.82)	**.014**
Stage		
I (reference)	1.00	
II	2.04 (0.92–4.53)	.079
II	3.19 (0.85–11.90)	.085
Systemic therapy		
No (reference)	1.00	
Yes	8.86 (3.94–19.91)	**<.001**
Group		
Non-Armenian (reference)		
Armenian	3.90 (1.52–10.01)	**.005**

Note: Bold indicates p value < 0.05.

comparisons. This could reveal molecular mechanisms and prognosticators important in PTC. Several somatic genetic alterations including those in BRAFV600E, RET/PTC, RAS and NTRK have fundamental roles in thyroid oncogenesis for PTC.[25,26] Rashid et al. reported on global prevalence of BRAFV600E mutation and reports a much higher prevalence of BRAFV600E mutation in the Asian series of PTC as compared to that in Western series.[27] Future prospective studies are needed to elicit potential genetic tumor differences or other contributing factors that lead to worse outcomes in this ethnic subpopulation.

Limitations of our study include the inherent retrospective nature and relatively small sample size. Although we identified higher recurrence risk and disease-related mortality for Armenian patients, the small sample available for multivariable analyses resulted in wide

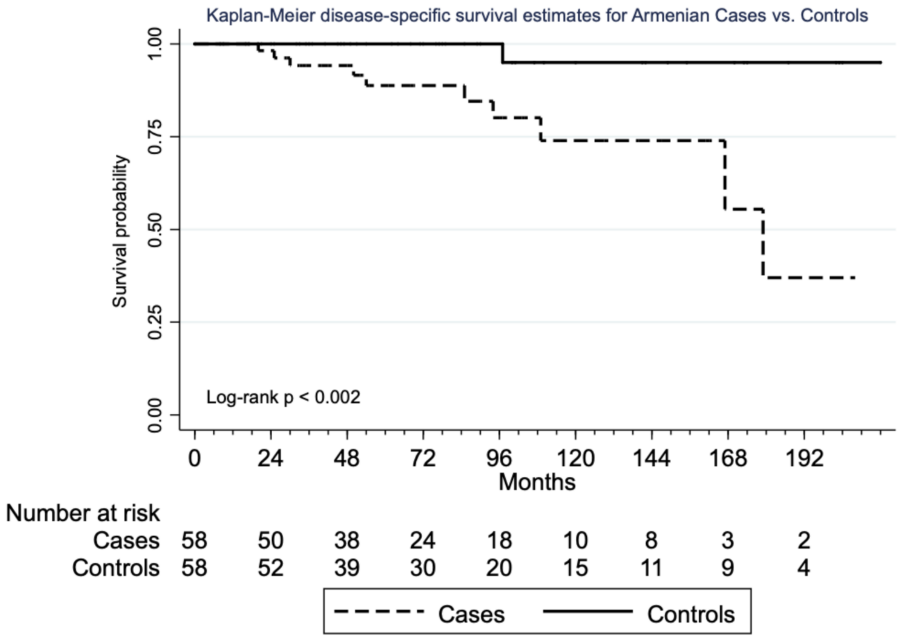

FIGURE 2 Kaplan–Meier estimate of disease-specific survival.

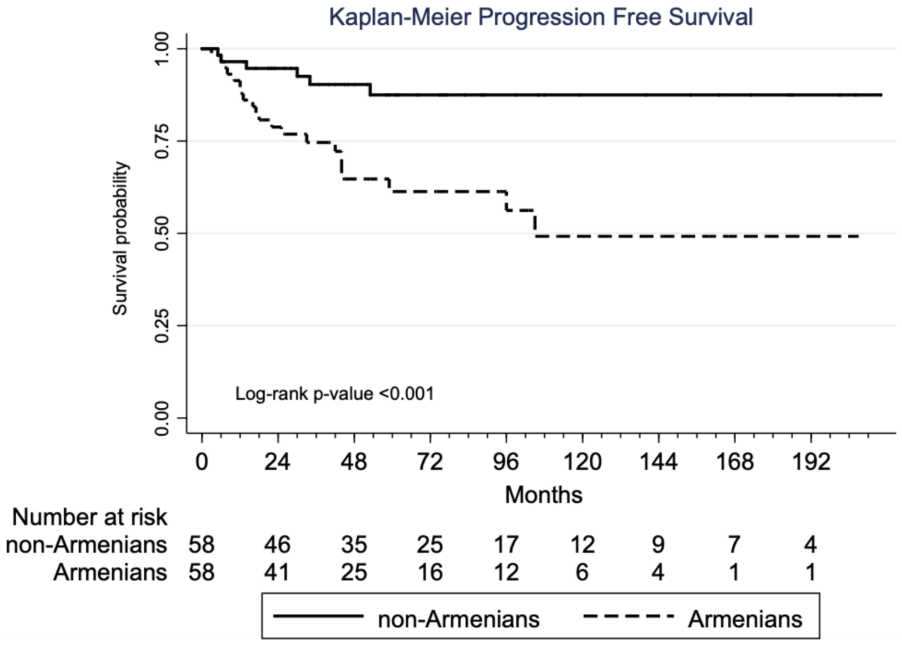

FIGURE 3 Kaplan–Meier estimate of progression-free survival.

confidence intervals for some of the hazard ratios reported. Consequently, we interpreted our findings with caution. Our conclusions need to be validated with larger patient cohorts through collaborative data registries. We considered an analysis of the California Cancer Registry to help validate our results, however, we learned that the registry only provided data for the 4 largest racial/ethnic groups in California which included Asian/Pacific Islander, Black, Hispanic, and non-Hispanic White. Hence, we were unable to tease out the Armenian ethnic subgroup from the non-Hispanic White population within the California Cancer Registry. We also made assumptions of Armenian heritage based on surnames which can be prone to error. In addition, the absence of long-term follow-up on most treated patients is another important limitation especially when examining a disease with an indolent course. These factors highlight the importance of investment in resources to support robust databases within cancer registries to help capture and follow-up on racial/ethnic minority groups with cancer diagnosis.

A strength of our study is a sincere attempt and to our knowledge the first in the U.S. to specifically look at this understudied subpopulation historically bundled into the non-Hispanic White population cohorts. Our geography allowed access to the Armenian thyroid cancer subpopulation for a more detailed study.

5 | CONCLUSION

Armenian PTC patients in our cancer center in Los Angeles County were found to have more aggressive disease than non-Armenians with higher rates of margin positivity, angioinvasion, and extrathyroidal extension. We also realized a higher incidence of locoregional and distant recurrent disease, and higher rate of disease-related mortality. Armenians had a higher incidence of treatment refractory disease with higher rates of both AWD and DOD. These differences corroborated our anecdotal clinical observations in practice but require further validation with larger patient cohorts through multi-institutional collaborations. There may be benefit realized in investments made in health care education, access, and delivery for this higher risk patient subpopulation. Armenian patients with PTC may warrant a more proactive and intensive approach in management and follow-up. Research is needed to further validate our institution's findings and explore the root causes for higher risk.

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CONFLICT OF INTEREST STATEMENT

The authors have no funding, financial relationships or conflicts of interest to declare.

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