ANTICANCER RESEARCH *39*: 949-956 (2019)
doi:10.21873/anticanres.13198

County Median Family Income Is an Independent Prognostic Factor for Stage IV Anaplastic Thyroid Cancer

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Abstract. *Background/Aim: Advanced anaplastic thyroid cancer (ATC) is a rare, but highly aggressive malignancy, and its prognostic factors need to be further explored. We examined socioeconomic factors' predictive effect for survival performance in stage IV ATC patients. Materials and Methods: Using the Surveillance, Epidemiology, and End Results database, we collected 1,048 cases with stage IV anaplastic thyroid cancer (ATC) from 2004 to 2015. Demographic, clinical, and socioeconomic factors were evaluated using univariate and multivariate analyses. Results: Median family income showed a significant effect on overall survival (OS) and cancer-specific survival (CSS) in univariate analysis. Median family income level was found to be an independent prognostic factor for OS after multivariate adjustment Multivariate analysis for CSS showed similar results. Conclusion: Family income level is an independent prognostic factor for stage IV ATC.*

Anaplastic thyroid cancer (ATC) is rare, but is one of the most lethal neoplasms in humans (1). Arising in the thyroid follicular epithelium, ATC is composed of undifferentiated cells that lack classic features of the thyroid gland and is, thus, also known as undifferentiated thyroid cancer (2). While it comprises of just 2% of all thyroid cancers, it accounts for up to 50% of mortality associated with thyroid cancer (3). Death often follows only a few months following diagnosis – median survival is 5 months (4), and less than 20% of patients survive for more than one year (5). This grim prognosis of ACT is likely due to the combination of occult symptoms, difficult diagnosis, and poor response to therapy (6, 7).

Considering the exceptionally aggressive nature of ATC, it is essential to identify its prognostic factors. Previous studies have confirmed that clinical factors including tumor size, presence of acute symptoms, extent of disease, leukocytosis, and treatment type impact survival (8-14). Recent studies have suggested that socioeconomic factors (SEF); such as marital status, insurance type, regional prosperity and educational attainment may also be important to consider as part of the prognosis of cancer disease (15-20). Studies on the importance of SEF in thyroid cancer, however, have so far mainly addressed well differentiated thyroid cancers rather than ATC (21-24).

In this study, we examined the impact of several SEFs, as well as traditional clinical factors on the survival of patients with stage IV ATC. Our aim was to further understand the role of common SEFs in the prognosis of advanced ATC and find more evidence for improving the quality of public health studies and associated policies.

Materials and Methods

Data source. All data was extracted from the 2017 Surveillance, Epidemiology, and the End Results (SEER) database of the National Cancer Institute using the SEER*Stat 8.3.5 software.

Since 1973, the SEER program has published epidemiological information on cancer statistics in the United States, covering approximately 28% of the population (25). This version of the database was based on November 2017 submission and includes treatment information regarding radiation and chemotherapy (https://seer.cancer.gov).

Criteria for inclusion and exclusion. We extracted data on stage IV anaplastic thyroid cancer cases from January 2004 through

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Key Words: Anaplastic thyroid cancer, socioeconomic factors, county level median family income, prognostic factor.

December 2015 (staging standard: American Joint Committee on Cancer staging manual 6th edition, [AJCC 6]). Cases were identified via the primary site label, "C73.9-Thyroid Gland." The histology type was defined by the International Classification of Diseases for the Oncology code: ICD-O-8020/3 to ICD-O-8022/3. Patients with an unknown marital status, 0 days of survival, and incomplete survival data were excluded.

Variables involved. Clinically relevant data including sex, age (<65 or ≥65 years), race (white or non-white), cancer stage (IVA, IVB, IVC and IV NOS [non-specific], AJCC 6), and treatment for thyroid cancer (including surgery, radiation, and chemotherapy) were involved.

Socioeconomic data regarding marital status and insurance type were also included. Single, widowed, separated, and divorced patients were categorized as unmarried. Insurance status included Medicaid, insurance other than Medicaid, unknown status, and uninsured. County-level socioeconomic factors were analyzed using updated county attributes (2012-2016 data). County-level high school education rate, unemployment rate, severity of language barriers, and median family income were categorized as Q1 (low performance, lower quartile), Q2 (medium performance, 50th percentile), or Q3 (high performance, upper quartile).

Statistical analysis. The primary outcomes were overall survival (OS) and cancer specific survival (CSS). Death from any reason was defined as an event in OS, while CSS event was defined as death due to ATC. Mean and standard deviation values were used to present continuous variables, and percentages were used to present categorical variables. We used the Kaplan-Meier method and log-rank tests for the univariate analysis. Demographic, clinical factors and statistically significant SEFs were further evaluated with multivariate Cox proportional hazard models. Two-sided *p*-values <0.05 were considered significant. All data was analyzed using SPSS 20.0 (Statistics Package for Social Science, Chicago, IL, USA).

Results

Patient characteristics. Our study included 1048 Stage IV ATC cases from 2004 to 2015. Information regarding demographics, clinical factors, and SEFs is listed in Table I. The mean age was 70.23±12.33 years. Patients were predominantly female (61.74%), white (79.10%) and ≥65 years old (66.70%). The proportion of patients with stage IVC (n=469, 44.75%) was nearly equivalent to the combined proportion of patients with IVA and IVB (10.69% and 35.21%, respectively). Nearly half of the patients received surgery, radiation, and/or chemotherapy (44.66%, 55.96%, and 41.60%, respectively). More than half of the patients (56.58%) were married at the time of diagnosis. Approximately 50% of patients had insurance other than Medicaid.

Overall survival. Among clinical factors, univariate analysis (Table II) showed that patients under 65 ($p<0.001$) and white patients ($p=0.041$) had better OS. Higher cancer stages were associated with a worse OS ($p<0.001$). Any type of treatment (surgery, chemotherapy, or radiation) seemed to favor improved OS ($p<0.001$). In the multivariate analysis, all factors mentioned above except for race remained significant (Table II). White patients did not show higher survival after adjustment using the Cox regression analysis ($p=0.39$).

In the univariate analysis (Table II), adverse prognostic factors included being unmarried ($p<0.001$) and living in counties with a lower average level of high school education ($p<0.001$) or with a higher unemployment rate ($p=0.024$). Patients living in counties with a lower quartile median family income were found to have a worse OS (Figure 1; 3-year survival in Q1, Q2 and Q3 groups were 0%, 9.35%, and 7.87%, respectively; $p=0.016$). Insurance type and county-level of language isolation did not affect OS ($p=0.594$ and 0.146, respectively). In the multivariate analysis, median family income remained as an independent prognostic factor (Q1 *vs*. Q2: hazard ratio (HR), 0.75; 95% confidence interval (CI), 0.60-0.94; $p=0.013$; Q1 *vs*. Q3: HR, 0.70; 95% CI, 0.54-0.91; $p=0.008$).

Table I. *Baseline demographic, clinical and socioeconomic features. SEER 2004-2015 (n=1048).*

Characteristic	No. of cases (%)
Total	1048
Age	
<65	349 (33%)
≥65	699 (67%)
Gender	
Female	647 (62%)
Male	401 (38%)
Race	
White	829 (79%)
Non-white	219 (21%)
AJCC Stage	
IVA	112 (11%)
IVB	369 (35%)
IVC	469 (45%)
IVNOS	98 (9%)
Primary surgery	
No surgery	574 (55%)
Surgery to thyroid	468 (45%)
Unknown	6 (1%)
Chemotherapy	
No known Tx	612 (58%)
Confirmed Tx	436 (42%)
Radiation simple	
No known Tx	472 (45%)
Confirmed Tx	576 (55%)
Marital status	
Unmarried	455 (43%)
Married	593 (57%)
Insurance	
Medicaid	126 (12%)
Insured, other than medicaid	526 (50%)
Uninsured	24 (2%)
Unknown status	372 (35%)

Tx, Treatment.

Table II. *Univariate and multivariate survival analyses for stage IV undifferentiated thyroid cancer patients' overall survival (OS) factors. SEER 2004-2015 (n=1048).*

Variables		Univariate analysis		Multivariate analysis		
	3-year OS	Log rank χ^2	*p*-Value	HR	95% CI	*p*-Value
Gender		1.31	0.252			
Female	7.59%			Reference		
Male	8.03%			1.01	0.87-1.16	0.913
Age		32.00	<0.001			
<65	11.74%			Reference		
≥65	5.92%			1.34	1.16-1.55	<0.001
Race		4.17	0.041			
White	8.56%			Reference		
Non-white	4.68%			0.93	0.79-1.09	0.388
AJCC Stage		134.57	<0.001			
IV A	25.08%			Reference		
IV B	9.98%			1.45	1.14-1.84	<0.001
IV C	1.50%			2.35	1.84-2.99	<0.001
IV NOS	6.80%			1.44	1.07-1.94	0.017
Primary surgery		146.12	<0.001			
No surgery	1.98%			Reference		
Surgery to thyroid	14.80%			0.53	0.46-0.61	<0.001
Unknown	0.00%			0.84	0.37-1.92	0.683
Chemotherapy		109.72	<0.001			
No known Tx	4.91%			Reference		
Confirmed Tx	11.78%			0.68	0.58-0.79	<0.001
Radiation simple		158.79	<0.001			
No known Tx	3.84%			Reference		
Confirmed Tx	10.93%			0.58	0.50-0.67	<0.001
Marital status		12.36	<0.001			
Unmarried	6.30%			Reference		
Married	9.00%			0.91	0.79-1.04	0.170
Insurance		1.90	0.594			
Medicaid	7.06%			N/A	N/A	N/A
Insured, other than medicaid	7.17%			N/A	N/A	N/A
Uninsured	13.97%			N/A	N/A	N/A
Unknown status	8.65%			N/A	N/A	N/A
High school education[§]		13.22	<0.001			
Q1	3.32%			Reference		
Q2	10.34%			0.93	0.75-1.15	0.494
Q3	6.85%			0.98	0.74-1.29	0.870
Unemployment		7.49	0.024			
Q1	6.96%			Reference		
Q2	8.99%			1.05	0.85-1.31	0.650
Q3	7.22%			1.08	0.83-1.40	0.557
Language isolation		3.84	0.146			
Q1	5.53%			N/A	N/A	N/A
Q2	9.33%			N/A	N/A	N/A
Q3	7.38%			N/A	N/A	N/A
Median family income		8.32	0.016			
Q1	0.00%			Reference		
Q2	9.35%			0.75	0.60-0.94	0.013
Q3	7.87%			0.70	0.54-0.91	0.008

Tx, Treatment. Socioeconomic factors which did not show statistical significance were not included in the multivariate analysis. [§]High school education rate, unemployment rate, language isolation rate and median family income level were categorized in three levels according to their performance percentile. Q1 represented the worst 25% among all counties, Q2 represented the middle 50% and Q3 represented the best 25%.

Cancer-specific survival. Among clinical factors, race, stage, surgery, chemotherapy and radiation therapy showed a significant effect on CSS in univariate analysis (Table III, $p=0.010$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). In the multivariate analysis, stage and treatments remained significant predictors of CSS (Table III).

In the univariate analysis, patients from counties with a lower quartile median family income had worse 3-year CCS

Table III. *Univariate and multivariate survival analysis for stage IV undifferentiated thyroid cancer patient's cancer specific survival (CSS) factors. SEER 2004-2015 (n=1048).*

Variables		Univariate analysis		Multivariate analysis		
	3-year CSS	Log rank χ^2	*p*-Value	HR	95% CI	*p*-Value
Gender		2.81	0.294			
Female	16.29%			Reference		
Male	16.99%			0.94	0.80-1.12	0.505
Age		2.85	0.092			
<65	15.41%			Reference		
>=65	18.03%			1.07	0.91-1.26	0.415
Race		6.704	0.010			
White	18.30%			Reference		
Non-white	10.41%			1.00	0.83-1.20	0.982
AJCC stage		141.21	<0.001			
IV A	46.46%			Reference		
IV B	20.50%			1.69	1.25-2.30	0.001
IV C	41.56%			3.08	2.26-4.19	<0.001
IV NOS	15.86%			1.75	1.20-2.54	0.003
Primary surgery		114.89	<0.001			
No surgery	5.15%			Reference		
Surgery to thyroid	27.86%			0.52	0.44-0.62	<0.001
Unknown	0.00%			0.88	0.36-2.17	0.783
Chemotherapy		56.52	<0.001			
No known Tx	14.70%			Reference		
Confirmed Tx	19.61%			0.71	0.60-0.86	<0.001
Radiation simple		105.26	<0.001			
No known Tx	10.36%			Reference		
Confirmed Tx	20.97%			0.58	0.49-0.69	<0.001
Marital status		14.49	<0.001			
Unmarried	14.37%			Reference		
Married	18.47%			0.83	0.71-0.98	0.027
Insurance		3.14	0.371			
Medicaid	0.00%			N/A	N/A	N/A
Insured, other than medicaid	15.37%			N/A	N/A	N/A
Uninsured	0.00%			N/A	N/A	N/A
Unknown status	17.92%			N/A	N/A	N/A
High school education		10.18	0.006			
Q1	10.02%			Reference		
Q2	20.89%			0.95	0.77-1.18	0.642
Q3	13.45%			0.99	0.76-1.29	0.932
Unemployment		4.72	0.094			
Q1	16.88%			N/A	N/A	N/A
Q2	18.37%			N/A	N/A	N/A
Q3	14.96%			N/A	N/A	N/A
Language Isolation		2.61	0.271			
Q1	15.91%			N/A	N/A	N/A
Q2	18.01%			N/A	N/A	N/A
Q3	14.66%			N/A	N/A	N/A
Median Family Income		6.51	0.039			
Q1	0.00%			Reference		
Q2	18.11%			0.74	0.57-0.96	0.021
Q3	17.79%			0.73	0.54-0.99	0.041

compared to the other groups (Figure 2; 3-year survival rates in Q1, Q2 and Q3 groups were 0%, 18.11%, and 17.79%, respectively; p=0.039). Patients who were married, resided in counties with higher levels of education and with a higher median family income exhibited a better CSS (p<0.001, p=0.006, and p=0.039, respectively). In the multivariate analysis, following an adjustment for demographic and clinical factors, marital status (Table III, unmarried *vs.* married: HR, 0.83, 95% CI 0.71-0.98, p=0.027) and the county median family income (Q1 *vs.* Q2: HR, 0.74; 95% CI, 0.57-0.96; p=0.021; Q1 *vs.* Q3: HR, 0.73; 95% CI, 0.54-0.99; p=0.041) remained independent predictors of CSS.

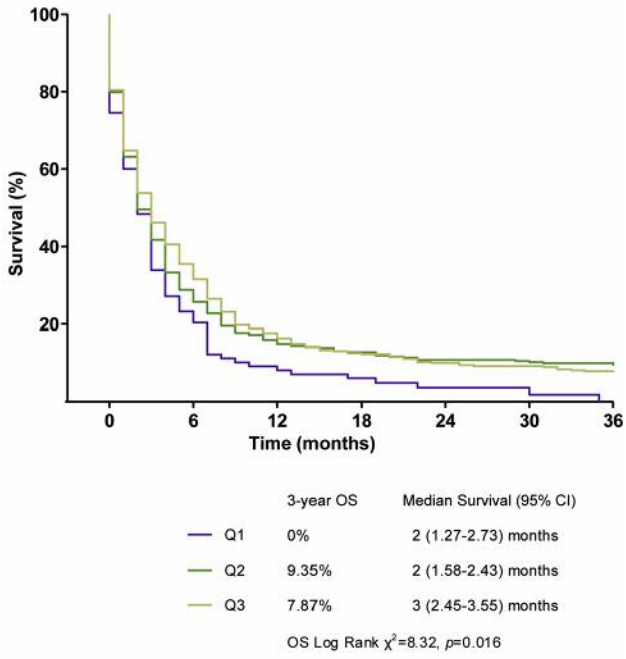

Figure 1. *Overall survival curves in patients with stage IV UTC.*

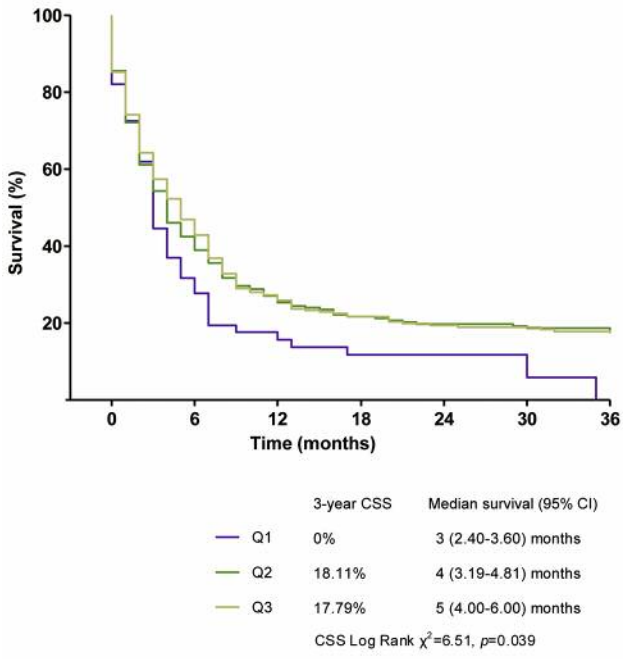

Figure 2. *Cancer-specific survival curves in patients with stage IV ATC.*

Discussion

Given that ATC is one of the most aggressive human malignancies, it is vital to identify relevant prognostic factors, both clinical and non-clinical (26, 27). In recent decades, many studies about socioeconomic factors' effect on disease and medical care have been conducted (28-30). Considering these facts, our study analyzed the impact of common SEFs on advanced ATC prognosis, and demonstrated that regional family income level is independently associated with OS and CSS in stage IV ATC.

After adjusting for sex, age, race, stage, and treatment type, we found that living in regions with a lower median family income relates with a worse prognosis of stage IV ATC patients. Many studies have shown that socioeconomic disparities negatively impact outcomes in cancer patients. In a large study of 229,195 breast cancer cases, county-level median family income was an independent prognostic factor for both overall survival and cancer-specific survival (31). A study of Chinese patients with thyroid cancer found that the per capita disposable income significantly affected the health-related quality of life (32). Similar findings have also been well-described in other common cancer types, including lung cancer, colorectal cancer, and prostate cancer (33-35). In the United States, Kaposi sarcoma as well as cancers of the larynx, cervix, penis, and liver showed the largest survival disparities were associated with the socioeconomic status of the patients (36). Regarding ATC, however, only few studies have previously noted the impact of poverty. In a study of 719 patients with ATC, Roche *et al*. found that poorer patients had a worse prognosis (35). Our study corroborated this finding.

There may be several explanations for the negative impact of poverty on survival in ATC. Firstly, financial difficulties may reflect lower levels of social support, which are important for determining health outcomes. Rice *et al*. studied the relationship between social network and cancer, and highlighted the importance of social network in providing economic resources, social involvement and tailored interventions (37). Secondly, the psychological impact of poverty may negatively impact health outcomes, as poorer individuals may experience decreased levels of autonomy and self-awareness (38). Thirdly, accessing more advanced treatment modalities is likely an obstacle for residents of low-income areas (39), while one study has shown that cancer survival rates increase with advances in treatment options (40). Fourthly, it has been proposed that poverty may be associated with a delayed diagnosis of cancer (36), but the evidence for this is conflicting. Singer et al have found poverty to be a significant prognostic factor even after adjusting for cancer stage (36), indicating that poverty affects the prognosis independent of delays in cancer

diagnosis. A study on lung cancer, however, has found that the impact of income on survival becomes insignificant after adjustment for clinical factors (33). Thus, further research delving into the relationship between income and cancer survival is necessary.

Marital status is a well-known SE prognostic factor in common cancer disease (17, 31, 41). In our study, patients who were unmarried showed lower OS and CSS in the univariate analysis. This effect was confirmed with the multivariate analysis of CSS. The other SEFs that we investigated, including the insurance type, the level of education, and the language isolation rate, did not show a significant impact on survival in stage IV ATC. Previous studies examining the influence of these SEFs on cancer survival have revealed controversial results. Niu *et al*. found that cancer patients on Medicaid had a worse prognosis than those on private insurance (42). Another study on childhood cancer has shown similar survival rates between patients on Medicaid and patients on private insurance (43). The level of education did not seem to impact breast cancer-specific survival in a large sample study (44). In another study, however, Williams *et al*. found that patients from counties with high rates of college education were more likely to accept radical cystectomy and have better OS (45). In a study on childhood acute myeloid leukemia, immigration-related features, including regional language isolation rate, were not independent prognostic factors (46). These results also highlight the need for further exploration of the effect of insurance type, level of education, and language isolation rate on ATC.

Our current study has several limitations. The SEER database provided us with the opportunity to carry out a relatively large sample study of ATC, but the database had inherent limitations. Firstly, since the database did not provide longitudinal data on the income status, we could not take into consideration the effect of changes in the income status on the patients' outcome. For instance, the median family income of a county may vary with time or patients may move to a county with a different median family income post-diagnosis. Secondly, the database provided county-level rather than individual-level information regarding the income, employment, and the level of education. Although county-level and individual-level variables are likely associated with one another, we are also very interested in the impact of personal socioeconomic status. Thirdly, SEER database only provided limited clinical information, excluding patient's comorbidities, chemotherapy plan/duration and radiation therapy details. Fourthly, DTC stage was defined using the AJCC 6 standard, however, using the latest AJCC 8 staging system would possibly be more reliable.

In conclusion, regional socioeconomic factors could affect stage IV ATC patients' survival performance. Patients from counties with the lowest median family income had a worse survival performance. Further studies with a larger sample size are necessary to further understand the relationship between regional economic status and ATC prognosis, and hopefully shift more health resources to be distributed to regions with a lower economic development level to improve ATC survival.

Conflicts of Interest

The Authors of this article have no conflicts of interest to declare.

Authors' Contributions

Mu Li and Lihong Huo did most of the study design and manuscript preparation. Mu Li and Rui Mao did most of the data analysis. Ying Ning and Pengyang Li participated in validating the data analysis. Sophie Gu, Ahmad Siddiqui and Nitin Trivedi contributed towards editing the manuscript. All authors contributed in the manuscript revision.

Acknowledgements

This study was not supported by any funding.

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Received December 27, 2018
Revised January 20, 2019
Accepted January 21, 2019