

Original Article

The association of low socioeconomic status with advanced stage thyroid cancer

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المخلص

أهداف البحث: تبحث هذه الدراسة في الصلة بين الحالة الاجتماعية والاقتصادية والمنخفضة وسرطان الغدة الدرقية المتقدم في وقت العرض. كما يقم المتغيرات الاجتماعية والاقتصادية التي قد تؤثر على مرحلة سرطان الغدة الدرقية عند العرض.

طرق البحث: أجريت هذه الدراسة الأترابية بأثر رجعي على جميع المرضى الذين يعانون من سرطان الغدة الدرقية بين يناير ٢٠١٦ وأبريل ٢٠٢٠. تم جمع البيانات باستخدام السجلات الطبية للمرضى والدراسات الاستقصائية المستندة إلى المقابلات. ومن أجل تقييم العوامل التي تتنبأ بمرحلة الإصابة بسرطان الغدة الدرقية المتقدم، تم جمع المؤشرات عن الحالة الاجتماعية والاقتصادية (مكان الإقامة، والمستوى التعليمي، والدخل، والحالة الاجتماعية).

النتائج: تم تسجيل ما مجموعه ٢٢٠ مريضاً مصاباً بسرطان الغدة الدرقية في هذه الدراسة. أما المرضى الذكور الذين هم أكبر من ٥٥ سنة، ويعيشون في المناطق الريفية، مع انخفاض المستوى التعليمي فقد كان هناك ارتباط بشكل كبير مع تأخر حضور مريض سرطان الغدة الدرقية للفحص. وأظهر التحليل المتعدد المتغيرات أن نوع الجنس (الرجال) والعمر (فوق ٥٥ سنة) كانا من أهم تنبؤات المرحلة المتقدمة من سرطان الغدة الدرقية. ومع ذلك، لم يكن هناك أي ارتباط بين الدخل ومرحلة سرطان الغدة الدرقية.

الاستنتاجات: وقد أظهرت هذه الدراسة أنه حتى في بلد مثل المملكة العربية السعودية مع نظام رعاية صحية قوي تموله الحكومة، يوجد تفاوت صحي في سرطان الغدة الدرقية. وقد وجدت دراساتنا أن العوامل الحالة الاجتماعية

والاقتصادية المنخفضة لها تأثير كبير على مرحلة سرطان الغدة الدرقية في وقت العرض. لم يكن للوضع الاقتصادي للمرضى أي تأثير على مرحلة سرطان الغدة الدرقية. وعلاوة على ذلك، تم تشخيص المرضى في مجموعات الحالة الاجتماعية والاقتصادية المنخفضة السفلى مع مراحل أكثر تقدماً في العرض.

الكلمات المفتاحية: الحالة الاجتماعية والاقتصادية؛ سرطان الغدة الدرقية؛ المرحلة؛ العرض؛ التشخيص.

Abstract

Objectives: This study investigates the link between low socioeconomic status (SES) and advanced thyroid cancer at the time of detection. It also assesses the socioeconomic variables that may potentially affect the stage of thyroid cancer at presentation.

Methods: This retrospective cohort study was conducted on patients with thyroid cancer between January 2016 and April 2020. The data were collected using the patients' medical records from the hospital information system (BESTcare) and through interview-based surveys. To assess the factors predicting the stage of advanced thyroid cancer, socioeconomic status (SES) predictors like area of residency, educational level, income, and marital status were collected.

Results: A total of 220 patients with thyroid cancer were included in this study. Male patients ($p = 0.025$), older than 55 years ($p < 0.001$), living in rural areas ($p = 0.002$), with low educational level ($p = 0.021$) were found to be significantly associated with advanced-stage thyroid cancer at presentation. Multivariate analysis showed that gender (men) and age (above 55 years) were significant predictors of advanced stage thyroid cancer. However, no

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association between income and the stage of thyroid cancer has been found in this study.

Conclusion: This study has shown that even in a country like KSA with a strong government-funded healthcare system, health disparity among people battling thyroid cancer exists. Our study has found that SES factors have a significant impact on the stage of thyroid cancer at the time of presentation, whereas the economic status of the patients had no impact on the stage of thyroid cancer. Furthermore, patients in lower SES groups were diagnosed with more advanced stages at presentation.

Keywords: Diagnosis; Presentation; Socioeconomic status; Stage; Thyroid cancer

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Introduction

Thyroid cancer is the most common endocrine cancer.¹ In KSA, It is the second most common cancer among females after breast cancer.² Although relatively uncommon in comparison to other types of cancer, it is the fastest-growing cancer in the last three decades.³ According to National Cancer Institution, the rate of new thyroid cancer cases has been rising on an average of 1.9% per year from 2007 to 2016, with an estimation of 52,070 new cases in 2019.⁴ Moreover, in KSA, one study found that the rate of incidence of thyroid cancer had increased 26-folds compared to a 10-folds increase in breast, colon, bladder, and uterine cancers from 1990 to 2016.⁵

As the accessibility to health care systems may differ between different patient groups, the timing of diagnosing and staging of thyroid cancer might be affected by these differences. A retrospective study comprising 9,585 children with well-differentiated thyroid cancer reported that families with lower income, lower education, and no insurance were associated with a higher stage of cancer at presentation and the time from diagnosis to treatment was longer.⁶ Another retrospective study done in two Canadian centres found that lower and higher socioeconomic status is related to a more advanced thyroid cancer stage at presentation and a higher incidence rate respectively.⁷ Furthermore, a retrospective chart review from New York found that tumour status and stages were more advanced in patients who visited public hospitals - most of whom did not have private insurance - than those who visited a university hospital for consultation.⁸ Additionally, a study conducted on 25,945 patients from the California Cancer Registry reported that patients with the lowest socioeconomic status (SES) presented with a metastatic disease more often than those with the highest SES.⁹

Furthermore, most of these studies were conducted on North Americans. Therefore, results might have been affected by the US health system (which is privately funded),

resulting in a higher number of low-income individuals having limited access to healthcare. However, the Saudi healthcare system is similar to the Canadian version. It provides healthcare through a government-funded system. The Saudi healthcare system provides coverage for all healthcare services which are considered a medical necessity for an individual; as such, care is provided as per the need rather than the financial status. However, as there is a dearth of relevant studies in KSA which explore the effects of SES on thyroid cancer presentation, this study aims to investigate the relationship between SES and thyroid cancer stage at presentation in KSA by using data from a tertiary health care hospital in Riyadh, KSA.

Materials and Methods

This retrospective cohort study uses data from ENT, General Surgery, and Oncology departments at King Abdulaziz Medical City in Riyadh, KSA. All thyroid cancer patients (245), from January 2016 until April 2020, were included in this study. The patients' electronic medical records were used to extract data such as gender, age, thyroid cancer type, and stage. Other factors like nationality, place, and location of residence, marital status, educational level, status of employment, monthly income, and quality of life were extracted using interview-based questionnaires through phone calls. Assessment of quality of life was based on Eastern Clinical Oncology Group (ECOG) performance status score. Non-respondents were given a second call on different occasions. However, those who did not respond despite the second call or patients who refused to participate were excluded from the analysis.

American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) classification system has been used to classify the patients to appropriate stages. To assess the factors predicting advanced thyroid cancer stage, stages I, II, and III were categorized into early-stage thyroid cancer, while stage IV was categorized into advanced stage thyroid cancer. In this study, the predictors of SES status were the location of residence (urbanization), educational level, income, and marital status. Those living in rural areas, having an educational level less than high school, income less than 5000SR/month, and those who were divorced/widowed were considered to have a low SES.

Variables including nationality, place of residence, and employment were used in bivariate logistic regression tests to investigate possible factors associated with advanced thyroid cancer apart from the SES variables defined above. Data were collected using an Excel worksheet by co-researchers. The study was approved by the Institutional Review Board of King Abdullah International Medical Research Centre (IRB No. RYD-20-419812-9633). Informed consent was obtained from all participants before the commencement of the survey. Participants' confidentiality was maintained by limiting access to the data to the principle and co-investigators. No incentives or financial payments have been provided for participation in the study.

Statistical Package for The Social Sciences (SPSS) Version 23 was used for all statistical analyses. Data were presented as frequency and percentages for categorical

variables (such as gender and nationality). Comparisons of early and advanced-stage thyroid cancer were performed using the Chi-square test. Factors predicting advanced stage thyroid cancer at the time of presentation have been tested using bivariate logistic regression. Multivariate logistic regression was used to determine socioeconomic factors predicting the advanced stage of thyroid cancer at presentation (Gender, age, location of residence, marital status, educational level, and Income). P-values of <0.05 were considered to indicate a statistically significant difference.

Results

A total of 220 thyroid cancer patients participated in this study with a response rate of 89.8%. We excluded 25 patients because of unresponsiveness or missing data. **Table 1** shows the socio-demographic profile of the participants. Among the participants, 51 (23.2%) were males and 169 (76.8%) were females. The participants were mostly younger than 45 years old, and 78 (35.5%) and 157 (71.4%) of the participants were single. As for nationality, 203 (92.3%) were Saudis and 17 (7.7%) were non-Saudi. A total of 167 participants (75.9%) were from the central region in KSA. Participants living in urban areas were 155 (70.5%). As for the educational level, 126 (57.3%) had education less than high school and 127 (57.7%) were not employed. Among the employed participants, 66 (30%) of them worked in the public sector. Regarding monthly income, 106 (48.2%) had an income less than 5000 SR/month.

Graph 1 demonstrates the performance status of patients with thyroid cancer, where 143 (65%) were ambulatory (had full activity), and 22 (10%) had limited self-care (or disabled). **Graph 2** demonstrates the type of cancer for the patients. The study found that the most common thyroid cancer was papillary thyroid carcinoma in 191 (87%) participants followed by follicular carcinoma in 14 (6%). Regarding the thyroid cancer stage at the time of presentation, 155 (70.5%) presented it at stage I, 40 (18.2%) at stage II, four (1.8%) at stage III, and 21 (3.5%) at stage IV. **Graph 3** displays the stage timing of thyroid cancer which indicates that 199 (90.5%) had early stage thyroid cancer at the time of presentation.

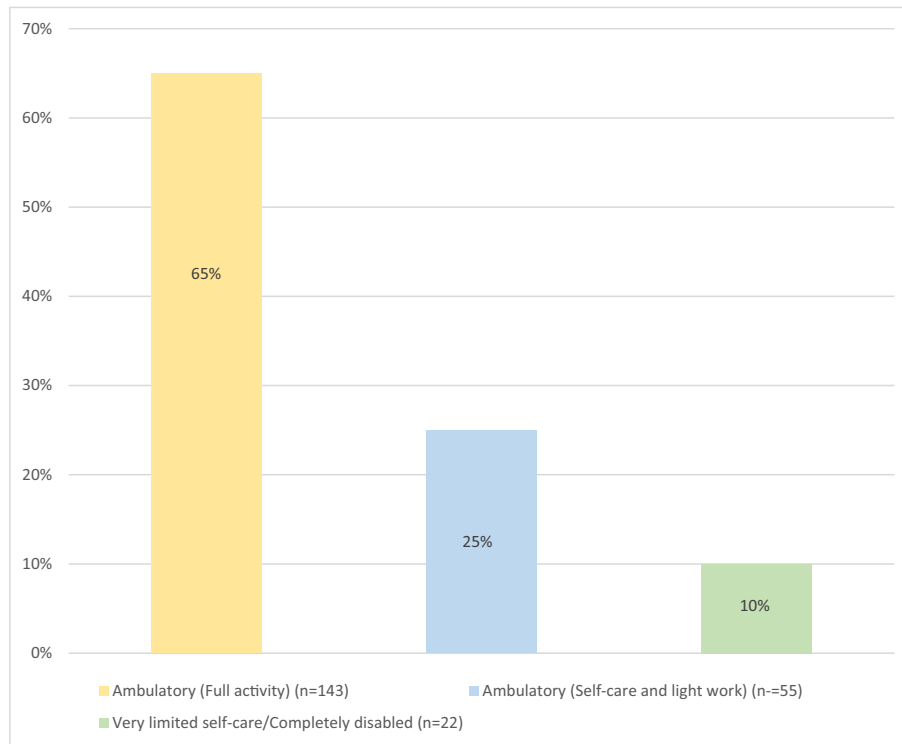
Table 2 shows the association between the stage of thyroid cancer at the time of presentation and socio-demographic variables. A significant association between gender and stage of cancer was noted. It was also observed that more males (17.6%) presented an advanced stage compared to females (7.1%) ($p = 0.025$). A significant association between age and stage of thyroid cancer was also found. Patients who were above 55 years (20.9%) had a higher rate of reporting an advanced stage compared to those who were under 45 years (1.3%) and those between 45 and 55 years (2%) ($p < 0.001$). Location was also found to be significantly linked to the stage of cancer at the time of presentation, those living in rural areas (29.2%) had higher rates of presenting with an advanced stage compared to those living in urban (7.1%) and suburban areas (7.3%) ($p = 0.002$). Educational level was also observed to be significantly correlated with the stage of cancer at the time of presentation. Those having educational qualifications less

Table 1: Socio-demographic profile of the participants (n = 220).

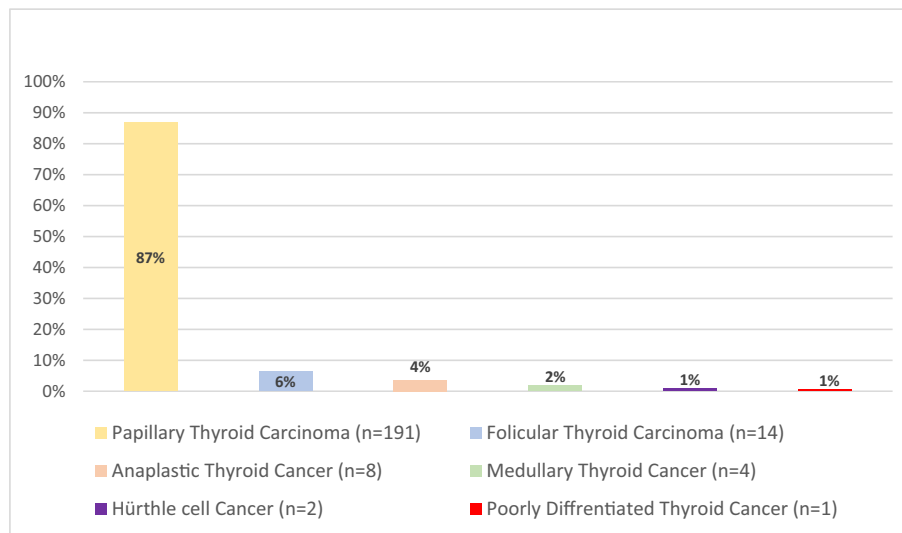
Demographical Characteristics	N	%
Gender		
Male	51	23.2
Female	169	76.8
Age (in years)		
<45	78	35.5
45–55	51	23.2
>55	91	41.4
Nationality		
Saudi	203	92.3
Non-Saudi	17	7.7
Place of Residence		
Northern Region	13	5.9
Central Region	167	75.9
East Region	21	9.5
Western Region	14	6.4
Southern Region	5	2.3
Location		
Urban	155	70.5
Suburban	41	18.6
Rural	24	10.9
Marital Status		
Married	26	11.8
Single	157	71.4
Divorced/Widowed	37	16.8
Educational Level		
Less than High School	126	57.3
High School	26	11.8
Bachelor's degree or higher	68	30.9
Job		
Employed	57	25.9
Not Employed	127	57.7
Retired	36	16.4
Job Place		
Government	66	30.0
Private	16	7.3
Not applicable	138	62.7
Income		
Less than 5000 SR/month	106	48.2
5000–10000 SR/month	60	27.3
10000–15000 SR/month	26	11.8
15000–20000 SR/Month	17	7.7
More than 20000 SR/month	11	5.0

than high school (14.3%), had a higher rate of presenting with an advanced stage compared to those having high school education (3.8%) and bachelor's degree (2.9%) ($p = 0.021$). No significant association was found with the following variables: nationality, place of residence, marital status, job, job place, income, or quality of life.

Table 3 displays the bivariate logistic regression to determine factors predicting patients with advanced thyroid cancer stages at the time of presentation. The following variables were tested: gender, age, nationality, place of residence, location, marital status, educational level, job, job place, and income. The following variables were observed to be significantly predictive of presenting with an advanced



Graph 1: Performance status of patients with thyroid cancer.

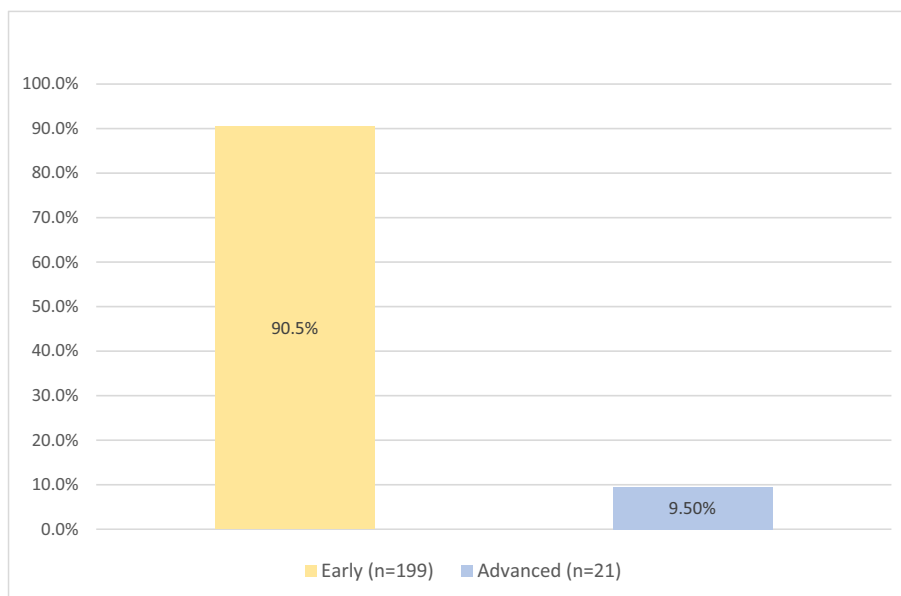


Graph 2: Types of thyroid cancer.

stage of thyroid cancer: age above 55 years, people living in rural areas, and retired patients. The following variables were observed to be significantly less associated with an advanced stage of thyroid cancer: females and patients with educational qualifications of bachelor's degree or higher.

Table 4 displays the multivariate logistic regression to determine factors predicting patients with advanced stage

of thyroid cancer at the time of presentation. The following variables were entered into the model: gender, age, location of living, educational level, and income. Age above 55 years was noted to be significantly predictive of presenting with an advanced stage of thyroid cancer, however, females were significantly less likely for such presentation.



Graph 3: Description of thyroid cancer stage.

Table 2: The association between stage of thyroid cancer at the time of presentation and socio-demographic variables.

Demographical Characteristics	Stage of Thyroid Cancer		P-Value
	Early	Advanced	
Gender			
Male	42 (82.4%)	9 (17.6%)	0.025 ^a
Female	157 (92.9%)	12 (7.1%)	
Age (in years)			
<45	77 (98.7%)	1 (1.3%)	<0.001 ^a
45 - 55	50 (98%)	1 (2%)	
>55	72 (79.1%)	19 (20.9%)	
Nationality			
Saudi	184 (90.6%)	19 (9.4%)	0.746
Non-Saudi	15 (88.2%)	2 (11.8%)	
Place of Residence			
Northern Region	11 (84.6%)	2 (15.4%)	0.281
Central Region	155 (92.8%)	12 (7.2%)	
East Region	18 (85.7%)	3 (14.3%)	
Western Region	11 (78.6%)	3 (21.4%)	
Southern Region	4 (80%)	1 (20%)	
Location			
Urban	144 (92.9%)	11 (7.1%)	0.002 ^a
Suburban	38 (92.7%)	3 (7.3%)	
Rural	17 (70.8%)	7 (29.2%)	
Marital Status			
Married	25 (96.2%)	1 (3.8%)	0.081
Single	144 (91.7%)	13 (8.3%)	
Divorced/Widowed	30 (81.1%)	7 (18.9%)	
Educational Level			
Less than High School	108 (85.7%)	18 (14.3%)	0.021 ^a
High School	25 (96.2%)	1 (3.8%)	
Bachelor's degree or higher	66 (97.1%)	2 (2.9%)	
Job			
Employed	55 (96.5%)	2 (3.5%)	0.101
Not Employed	114 (89.8%)	13 (10.2%)	
Retired	30 (83.3%)	6 (16.7%)	

Table 2 (continued)

Demographical Characteristics	Stage of Thyroid Cancer		P-Value
	Early	Advanced	
Job Place			
Government	59 (89.4%)	7 (10.6%)	0.598
Private	15 (93.8%)	1 (6.3%)	
Income			
Less than 5000 SR/month	90 (84.9%)	16 (15.1%)	0.820
5000–10000 SR/month	57 (95%)	3 (5%)	
10000–15000 SR/month	24 (92.3%)	2 (7.7%)	
15000–20000 SR/Month	17 (100%)	0.00	
More than 20000 SR/month	11 (100%)	0.00	

^a Significant at level 0.05.**Table 3: Bivariate logistic regression (Factors predicting advanced stage thyroid cancer at presentation).**

Demographic Variable	P-Value	Crude Odds Ratio	Confidence Interval	
Gender (Female vs Male)	0.03 ^a	0.357	0.141	0.903
Age (in years) (<45 is the Referent)				
45 - 55	0.76	—	—	—
>55	0.004 ^a	20.319	2.652	155.706
Nationality (Non-Saudi vs Saudi)	0.75	—	—	—
Place of Residence (Northern Region is the Referent)				
Central Region	0.30	—	—	—
East Region	0.93	—	—	—
Western Region	0.69	—	—	—
Southern Region	0.81	—	—	—
Location (urban is the Referent)				
Suburban	0.96	—	—	—
Rural	0.002 ^a	5.39	1.844	15.757
Marital Status (Married is the Referent)				
Single	0.44	—	—	—
Divorced/Widowed	0.11	—	—	—
Educational Level (Less than High School is the Referent)				
High School	0.18	—	—	—
Bachelor's/Higher	0.025 ^a	0.182	0.041	0.809
Job (Employed is the Referent)				
Not Employed	0.14	—	—	—
Retired	0.044 ^a	5.5	1.045	28.955
Job Place (Private vs Government)	0.60	—	—	—
Income (Less than 5000 SR/month is the Referent)				
5000–10000 SR/month	0.06	—	—	—
10000–15000 SR/month	0.33	—	—	—
15000–20000 SR/Month	0.998	—	—	—
More than 20000 SR/month	0.999	—	—	—

^a Significant at level 0.05.**Table 4: Multivariate logistic regression (Factors predicting advanced stage thyroid cancer at presentation).**

Demographics	P-Value	Adjusted Odds Ratio	Confidence Interval	
Gender (Female vs Male)	0.039 ^a	0.255	0.07	0.934
Age in years (<45 is the Referent)				
45 - 55	0.571	—	—	—
>55	0.025 ^a	22.274	1.47	337.559
Location (urban is the Referent)				
Suburban	0.85	—	—	—
Rural	0.1	—	—	—
Marital Status (Married is the Referent)				
Single	0.85	—	—	—
Divorced/Widowed	0.3	—	—	—

(continued on next page)

Table 4 (continued)

Demographics	P-Value	Adjusted Odds Ratio	Confidence Interval
Educational Level (Less than High School is the Referent)			
High School	0.99	—	—
Bachelor's/Higher	0.27	—	—
Income (Less than 5000 SR/month is the Referent)			
5000–10000 SR/month	0.53	—	—
10000–15000 SR/month	0.999	—	—
15000–20000 SR/Month	0.998	—	—
More than 20000 SR/month	0.999	—	—

^a Significant at level 0.05.

Discussion

The causes behind presenting with advanced stage thyroid cancer are complex and involve many factors. The stage at presentation is known to have a very strong survival predictor, especially in follicular, medullary, and anaplastic tumours.¹⁰ This study aims to investigate the relationship between SES and thyroid cancer stage at presentation in KSA. Our paper demonstrates significant associations between different SES factors and stage of thyroid cancer at presentation. Participants who were male, aged above 55 years, living in rural areas, and having an educational level less than high school, were found to be important predictors of advanced stage thyroid cancer. However, income and marital status were not found to be substantial factors for the same.

It was found that age and gender have a strong correlation with the incidence as well as the stage of thyroid cancer at presentation.^{10–12} Our results confirmed that those above 55 years and male patients have a higher rate of presenting with an advanced stage. In another study, it was also found that patients with advanced stages were significantly older than patients with early stages.⁸ Women were found to be at a higher risk of developing thyroid cancer than men. However, they tend to be diagnosed earlier since they present with thyroid symptoms such as menstrual irregularities or infertility and therefore, usually undergo more radiological testing, especially in gynaecologic and obstetric settings.^{13,14} However, men have a lower incidence of thyroid cancer but tend to present at later stages (stages III or IV) and with more aggressive thyroid carcinoma.^{12,15} Age and gender also play an important role in the prognosis and survival of the patients. Studies have found that older patients and males have a worse prognosis of the disease.^{8–11} However, another study reported that the difference between males and females in the survival rate was small which indicates that gender is a weak prognostic predictor.¹⁰

Few studies have investigated the SES factors associated with advanced thyroid cancer at presentation. It was found that income is one of the major predictors, on which most of the studies depend to define the level of SES.^{6,7,15} Low monthly income is a predictor of advanced stage thyroid cancer.^{15,16} It has also been associated with worse prognosis and outcome even after adjusting for the cancer

stage.^{17–19} However, it is worth mentioning that all those studies were conducted in non-funded hospital systems. In our study, no association between monthly income and thyroid cancer stage is found. This disparity might be explained by the difference in KSA's healthcare system, which is a government-funded system with zero costs. The Canadian healthcare system is similar to the Saudi healthcare system; however, interestingly, a more advanced stage of thyroid cancer was found in patients with low monthly income, which was attributed to non-medical costs such as transportations and parking.⁷ Thus, we may conclude that low income might not be a true risk factor for having advanced thyroid cancer, but it is probably a barrier to early detection of the disease.

Among SES factors, living in rural areas was a predictor of advanced stage thyroid cancer. In the existing literature, no thyroid cancer study assessed the effect of urbanization level on cancer stage; however, its impact on cancer incidence has been reported. Studies indicate that thyroid cancer was less prevalent in rural areas compared to cities.^{14,20} This difference might be influenced by the proximity of more tertiary centres and advanced healthcare in cities leading to earlier diagnosis and better prognosis.^{14,20}

Having an education level less than high school was also a predictor of advanced stage thyroid cancer. In a retrospective study done involving paediatric patients afflicted with thyroid cancer, it has been found that the lower educational quartile of their family was linked with a higher stage at diagnosis.⁶ The educational level also has an impact on cancer incidence. Patients with higher educational levels are at an increased risk for papillary thyroid carcinoma and have a higher rate of receiving diagnostic thyroid ultrasounds.¹³ According to a cohort study, a higher education level is linked to thyroid cancer as an independent risk factor.²¹

Marital status is one of the popular factors that generally influence cancer prognosis.^{18,22,23} The overall, as well as specific cancer survival, were confirmed to be favourable in married patients.¹⁷ Even though our study did not show any significant association with marital status, it was observed that patients who are married present with early stages frequently than the others. Multiple hypotheses have been proposed in other studies explaining the positive association of being married with a better survival rate. For example, the effect of a high mean age on the diagnosis of thyroid cancer is present in a large

number of widowed and divorced patients.²⁴ Furthermore, married patients are considered to have better financial status, social support, housing, lifestyle, and access to healthcare.²⁵

Moreover, it has been observed that SES disparities have a huge impact on the difference in healthcare quality and accessibility.^{6,26,27} Disparities in patient's healthcare access and use, particularly in preventive health services such as cancer screening are contributing factors for the differences in the incidence rate and the cancer stage at presentation.^{6,26–28} Other non-thyroid cancer studies also indicated the strong association between the advanced cancer stage at presentation and low SES.^{27–29} It was also noted that the distance of the location of residence from primary healthcare facility was linked with more advanced stage at diagnosis and worse outcomes.^{27–29} In a breast cancer study by J.H. Silber et al., it was concluded that the reason for the advanced stage at diagnosis in lower SES is the low quality and thoroughness of preventive care in screening and managing their comorbid conditions in breast cancer prognosis.²⁷

Strengths and limitations

There are several limitations to our study. The results in this study reflect the data from a single tertiary centre in KSA; as such, it might be difficult for the findings to be generalized for all cancer cases in the country. Data about SES indicators were collected using questionnaires rather than from a national database which could be subjected to response bias. To minimize this, all questionnaires were filled by the co-investigators through phone interviews. Additionally, our study did not examine patient's comorbidities and other risk factors. In this study, almost all patients were from the same region. Hence, they were unlikely to have differences in environmental exposure such as radiation.

Despite these potential limitations, our study has multiple strengths. To the best of our knowledge, this is the first study assessing the effect of SES on the stage of thyroid cancer in KSA. Furthermore, this study unlike most other studies on thyroid cancer has been conducted in a country with a government-funded healthcare system. Additionally, it is one of the very few studies that have assessed the association between SES and thyroid stage in the adult population while most research studied SES with thyroid cancer incidence. Moreover, this study included most factors indicating SES (urbanization, marital status, educational level, and monthly income) allowing a more comprehensive assessment of SES's effect on the thyroid cancer stage.

Conclusion

In conclusion, even in KSA, with the government-funded healthcare system, health disparity in thyroid cancer does exist. In line with prior studies, our study found that the SES factors have a significant impact on thyroid cancer stage at presentation except for the patient's income, which showed to have no role. Furthermore, patients in lower SES groups were diagnosed with more advanced stages at presentation. Therefore, larger studies should be conducted on this topic and further studies should be done to assess the mortality, recurrence rates, and prognosis of each variable. Furthermore, the effect of

other health risks on the stage at presentation was not examined and should be investigated in future studies.

Source of funding

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This research was evaluated and approved by King Abdullah International Medical Research Center (KAIMRC) (Date: 01/01/2020 No. RYD-20-419812-9633).

Authors contributions

AAA conceptualised and designed the study. He collected, and organized the data as well as wrote the initial and final draft of the article. YAA contributed to the acquisition, analysis, and interpretation of data, and wrote the initial and final draft of the article. MAE designed the study, and supervised, the article writing. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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