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Association of pre-op TSH levels with Thyroid Carcinoma in a Tertiary Care Setup in Karachi, Pakistan

Tehmina Junaid, Areej Fatimah Iqrar Siddiqui, Tariq Zahid Khan, Zeba Ahmed, Basit Arif, Sana Kazmi, Muhammad Umair Tahseen

ABSTRACT

Objectives: This study aimed to explore the relationship between pre-operative TSH levels and the presence of thyroid cancer in patients with nodular thyroid disease in the Pakistani population, using data gathered from patients treated at Dr. Ruth K. M. Pfau Civil Hospital Karachi.

Study Design & Setting: A cross-sectional study was conducted at the Dow University of Health Sciences and Dr. Ruth K. M. Pfau Civil Hospital Karachi from January 2022 to December 2022.

Methodology: Patients with thyroid swellings (presenting with either solitary nodules or with multinodular goiter), both benign as well as suspected/confirmed malignancy based on FNAC results were recruited in the study. Preoperative TSH levels, along with other clinical data, were collected. Thyroidectomy was carried out in patients fulfilling the criteria for surgery, with specimens sent for histopathology. An independent t-test was used to compare TSH levels between malignant and benign nodules.

Results: A total of 82 patients were enrolled. Malignancy was confirmed in 41.5% (25 papillary carcinoma, 9 follicular carcinoma). Significantly higher mean TSH levels were observed in patients with malignant nodules (4.76 IU/mL) compared to those with benign nodules (2.48 IU/mL) ($p < 0.001$).

Conclusion: This study suggests a potential association between elevated pre-operative TSH levels and thyroid cancer in the Pakistani population. These findings warrant further investigation to explore causality and potential underlying mechanisms. The study highlights the value of TSH monitoring, particularly in resource-constrained settings.

Keywords: Thyroid carcinoma, TSH, Pakistan, South Asia.

How to cite this Article:
Junaid T, Siddiqui AFI, Khan TZ, Ahmed Z, Arif B, Kazmi S, Tahseen MU. Association of pre-op TSH levels with Thyroid Carcinoma in a Tertiary Care Setup in Karachi, Pak J Bahria Uni Med Dental Coll. 2024;14(4):240-245 DOI: https://doi.org/10.51985/JBUMDC2024366

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Received: 29-04-2024
Accepted: 11-09-2024
1st Revision 04-06-2024
2nd Revision 05-07-2024
3rd Revision 21-08-2024

INTRODUCTION:

Thyroid carcinoma stands as the most prevalent type of endocrine malignancy, potentially compromising thyroid hormone production and causing health problems. This malignant tumor can arise from different cell types in the thyroid, requiring specific tests and treatments depending on its origin and severity. It ranks as the seventh most prevalent cancer in women globally, an estimated 586,202 individuals were diagnosed with thyroid cancer in 2020. In 2023, approximately 43,720 adults in the United States are expected to receive a thyroid cancer diagnosis, with 12,540 cases among men and 31,180 among women. In Pakistan, thyroid carcinoma remains a health burden with being in twenty most prevalent cancers in the country.

Until recently, thyroid cancer experienced a notable surge in diagnoses in the United States, attributed in part to the enhanced sensitivity of diagnostic tests leading to the detection of smaller cancers. However, since 2014, there has been an annual decrease of around 2% in the incidence rate, coinciding with the adoption of newer diagnostic criteria.

Thyroid cancer often manifests at a younger age compared to other adult cancers, with white individuals being 70% more likely to be diagnosed than their Black counterparts, who exhibit the lowest incidence rates. The projected toll

for 2023 includes an estimated 2,120 deaths in the United States, with 970 among men and 1,150 among women. Despite a stable death rate between 2011 and 2020, women are three times more likely to be diagnosed with thyroid cancer than men. Interestingly, while men and women face similar mortality rates, men tend to have a less favorable prognosis than women upon receiving a thyroid cancer diagnosis, highlighting gender-specific differences in outcomes. In 2020, an estimated 43,646 people worldwide succumbed to thyroid cancer .

Recent studies suggest a potential link between TSH and thyroid carcinoma progression.[1] It has been reported that higher pre-operative TSH levels might be associated with worse overall and disease-free survival in papillary thyroid carcinoma patients after surgery.[2] This adds to the evidence suggesting a link between TSH and disease aggressiveness. It has also been reported that high pre-operative TSH levels can predict disease progression in patients with papillary thyroid carcinoma undergoing active surveillance. This highlights the potential role of TSH monitoring in managing this group of patients.[3] While several studies have linked higher TSH levels in thyroid nodules to a higher risk of malignancy, even within the normal range, this hasn't been thoroughly investigated in South Asian populations. To address this gap, we set out to explore the relationship between pre-operative TSH levels and thyroid cancer in this specific population.

METHODOLOGY:

This study, conducted at the Dow University of Health Sciences and Dr Ruth K. M. Pfau Civil Hospital Karachi over a one-year period, from January 2022 to December 2022, employed a cross-sectional observational design within the department of ENT and Head and Neck Surgery. Ethical approval was secured through the Institutional Review Board.

Participants were recruited from patients presenting to the ENT OPD of Dr. Ruth K. M. Pfau, Civil Hospital Karachi, with thyroid swellings (presenting as either solitary nodules or multinodular goiter), which included both benign cases as well as suspected/confirmed malignancy based on FNAC results. All the individuals exhibiting thyroid swellings underwent pre-operative evaluation, including T-3, T-4, and TSH level measurement, neck ultrasonography, and FNAC. Those meeting surgical criteria underwent thyroidectomy, with subsequent histopathological examination of the excised tissue.

Inclusion criteria for the study stipulated informed consent, age between 15 and 65 years, and those patients who presented with benign thyroid swellings, and were planned to undergo thyroidectomy, as well as patients with suspected thyroid malignancy based on FNAC results. Conversely, exclusion criteria encompassed pregnancy, Bethesda 1/Thy 1 cytology on FNAC, and prior use of thyroxine or anti-thyroid medications.

This approach ensured the recruitment of a representative sample while minimizing potential confounding factors, thereby strengthening the study's internal validity and generalizability. The sample size of 61 was calculated using web based sample size calculator. The confidence interval was kept at 95%, and the margin of error was kept 7% with a population proportion of 8.4%. However, a total of 82 patients with thyroid swellings were enrolled.

Data Analysis was performed using SPSS version 24.0. An independent t-test was used to find out if there is any relationship between the presence of malignant and benign nodules with the TSH value.

RESULTS:

This study investigated the characteristics and outcomes of 82 patients undergoing evaluation for thyroid nodules. The average age of participants was 40.2 ±7.56 Standard Deviation (SD), with a predominance of females (72%) compared to males (28%).

A total of 41.5% (25 patients with papillary carcinoma + 9 patients with follicular carcinoma) of the 82 patients were diagnosed with malignant nodules. Papillary carcinoma was the most prevalent type of cancer, affecting 30.5% (25 out of 82 patients) of the study population. Follicular carcinoma was identified in 11% (9 out of 82 patients) of the participants.

58.5% (10 patients with solitary nodules + 38 with multinodular goiter) of the patients had benign nodules. Solitary nodules were found in 12.2% (10 out of 82 patients). Multinodular goiter was the most common benign condition, affecting 46.3% (38 out of 82 patients) of the participants.

Importantly, a significant association emerged between TSH levels and the presence of malignant nodules. In patients with thyroid malignancy, the mean TSH level was 4.76 IU/mL ± 2.43 SD, while it was 2.48 IU/mL ± 1.65 SD in patients with benign disease (P = 0.001). Results are shown in Figure 1. Patients diagnosed with papillary carcinoma (30.5%) or follicular carcinoma (11%) had higher average TSH levels compared to those with benign nodules (solitary nodule: 12.2% and multinodular goiter: 46.3%). The majority of patients who underwent surgery received total thyroid-ectomy (87.8%).

a: The chi-square test was used to compare the relationship between the gender, FNAC, and ultrasound findings with the TSH value

b: An independent t-test was used to find out if there is any relationship between the presence of malignant and benign nodules with the pre-operative TSH value. P-value <0.001 is significant

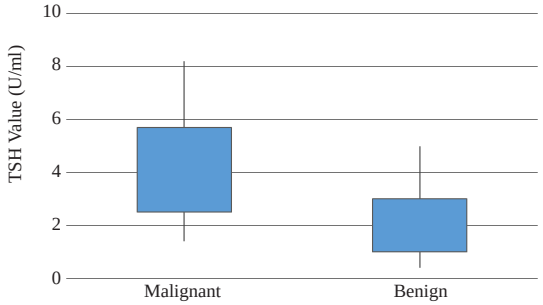
DISCUSSION:

Our cross-sectional study in the Pakistani population of Karachi, Sindh using data gathered from patients treated at Dr. Ruth K. M. Pfau Civil Hospital Karachi, adds another

Table 1: Number and Percentage of patients according to sample size, ultrasound findings, FNAC, Diagnosis of carcinoma type and surgical procedure performed.

N	82	%	P-value
Age	40.2±7.56 (26-59)		
Gender			0.348[a]
Male	23	28	
Female	59	72	
TSH (IU/mL)	3.05±1.74		
Ultrasound Findings (TIRADS Classification)			0.346[a]
1	0	0	
2	2	2.4	
3	26	31.7	
4	25	30.5	
5	21	25.6	
6	5	6.1	
7	3	3.7	
FNAC (Bethesda Classification)			0.561[a]
I	1	1.2	
II	4	4.9	
III	48	58.5	
IV	15	18.3	
V	11	13.4	
Diagnosis			<0.001[b]
Solitary Nodule	10	12.2	
Multinodular Goitre	38	46.3	
Papillary Carcinoma	25	30.5	
Follicular Carcinoma	9	11	
Surgery Performed			
Hemithyroidectomy	10	12.2	
Total Thyroidectomy	72	87.8	

Graph 1: Number and Percentage of patients according to sample size, ultrasound findings, FNAC, Diagnosis of carcinoma type and surgical procedure performed.



crucial piece to the puzzle of understanding the relationship between TSH levels and thyroid carcinoma. Our findings suggest intriguing trends that warrant further exploration. The observed difference in mean age between malignant (42.35 years +/- 8.29 SD) and benign (38.75 years) cases aligns with existing literature. Studies report a higher incidence of thyroid cancer in individuals aged 40-55 years.[4,5] Interestingly, the gender distribution in both groups (approximately 70% female, 30% male) reflects the well-established higher prevalence of thyroid cancer in women.[6]

Our study found a significantly higher prevalence of multinodular goiter (MNG) compared to solitary nodules within the benign nodule group. This aligns with previous research suggesting MNG is the most common thyroid disorder.[8,9,10]

Our investigation revealed a malignancy rate of 41.46%, consistent with previous research indicating a diverse range of malignancy prevalence in thyroid nodules, spanning from 5% to 44% across various study cohorts. Nonetheless, it is crucial to acknowledge that this figure may not accurately depict the actual prevalence of malignancy within the broader population.

While our findings align with existing literature on the variability of malignancy rates in thyroid nodules, several factors merit consideration when interpreting these results. Firstly, the heterogeneity of study populations and methodologies employed in previous research can contribute to discrepancies in reported malignancy rates. Variations in patient demographics, geographic locations, and diagnostic criteria may influence the observed prevalence of thyroid cancer across different studies.

Furthermore, the inherent limitations of our study design, such as the reliance on a specific patient cohort and diagnostic modalities, may impact the generalizability of our findings to the broader population. Our inclusion criteria, which targeted patients with suspected thyroid malignancy based on fine-needle aspiration cytology (FNAC), inherently skewed our sample towards individuals with a higher likelihood of cancer, potentially inflating the observed malignancy rate.

Additionally, referral biases within the healthcare system, particularly within the ear, nose, and throat (ENT) specialty, may influence the composition of our study population and contribute to the observed malignancy rate. Patients referred to specialized centers for further evaluation and management of thyroid nodules may exhibit different clinical characteristics and disease profiles compared to individuals in the general population, leading to potential overestimation of malignancy prevalence.

Population-based studies suggest a lower true prevalence, typically between 5% and 10%.[16,17] This disparity from the existing population-based malignancy rate can be attributed to the fact that the inclusion criterion of our study inherently followed patients with suspected thyroid malignancy based on FNAC, a population with a higher pre-test probability of cancer. FNAs are not routinely performed on all thyroid nodules, and those deemed suspicious enough to warrant an FNA are more likely to harbor malignancy compared to the general population with thyroid nodules.[18] Additionally, referral patterns within the ENT ward might have introduced

patients with more concerning features, contributing to the observed high cancer rate.

Of the malignant cases in our study (34), 73.5% (25) were cases of papillary carcinoma, and 26.4% (9) cases of follicular carcinoma. This finding aligns with papillary carcinoma being reported as the most prevalent thyroid carcinoma.[19,20]

The most striking finding is the significant difference in mean TSH levels between the two groups, with malignant cases exhibiting a considerably higher average TSH (4.17) compared to benign cases (2.27). This observation aligns with prior research suggesting an association between subclinical hypothyroidism (elevated TSH with normal thyroid hormone levels) and an increased risk of thyroid cancer.[9,21]

A study investigating the potential role of TSH in the development of thyroid carcinoma suggested that TSH stimulation might promote the development of undetectable thyroid microcarcinomas into larger, identifiable tumors.[7] It has also been reported that activating mutations in the TSH receptor gene are detected within certain differentiated thyroid carcinomas. These cancers are characterized by a twofold abnormality: elevated basal adenyl cyclase activity and diminished responsiveness to TSH stimulation.[22]

Several noteworthy studies bolster our observations. A large-scale meta-analysis by Hu et al (2019)[23] encompassing over 14 million individuals identified a clear dose-response relationship between elevated TSH and thyroid cancer risk, particularly for papillary thyroid carcinoma, the most common type. Similarly, another study investigated the relationship between TSH serum concentrations and thyroid malignancy. Their analysis suggests a link between higher TSH levels and an increased risk of thyroid carcinoma.[24] Additionally, a separate study involving over 11,000 patients observed an approximate 11% rise in the likelihood of papillary thyroid carcinoma (PTC) for every milliunit per liter (mIU/L) increase in TSH levels.[25]

Although age, gender, and the existence of thyroid nodules are acknowledged as established risk factors for thyroid cancer, the intricate interplay among these factors, cancer onset, and TSH levels continues to be subject to ongoing scrutiny. Our results reaffirm this stance, emphasizing the viability of TSH as an accessible and economical screening tool, particularly in resource-limited contexts such as Pakistan.

Understanding the precise relationship between demographic variables, thyroid nodules, TSH levels, and cancer development presents a multifaceted challenge that necessitates comprehensive investigation. While age and gender have been consistently identified as significant risk factors for thyroid cancer, the mechanistic links between these factors and TSH dynamics remain elusive. Unraveling these complexities requires interdisciplinary approaches that integrate clinical, epidemiological, and molecular perspectives to elucidate the underlying pathophysiological mechanisms driving thyroid carcinogenesis.

Moreover, our findings underscore the pivotal role of TSH assessment in early detection and risk stratification for thyroid cancer, particularly in resource-constrained settings where access to advanced diagnostic modalities may be limited. By leveraging TSH as a screening biomarker, healthcare providers can identify individuals at heightened risk of thyroid malignancy and implement timely interventions to mitigate disease progression and improve clinical outcomes.

Furthermore, the cost-effectiveness and simplicity of TSH testing render it an attractive option for population-based screening programs aimed at reducing the burden of thyroid cancer in high-risk populations such as Pakistan. Integrating TSH assessment into routine healthcare protocols can facilitate early diagnosis, enhance patient prognosis, and optimize healthcare resource allocation, ultimately alleviating the socioeconomic burden associated with advanced-stage thyroid cancer.

Furthermore, our study sheds light on the specific context of the Pakistani population. Previous research suggests that the prevalence of thyroid disorders, including thyroid cancer, might be higher in South Asia compared to Western countries. A study by Bukhari et al. (2009) reported a higher incidence of thyroid cancer in Pakistan compared to the United States, potentially due to factors like iodine deficiency and genetic susceptibility. Considering this context, our findings become even more compelling, emphasizing the importance of vigilant TSH monitoring and early intervention for the Pakistani population.

The distribution of FNAC categories aligns with expectations in our study, with the majority of benign diagnoses (62.9%) falling under the Bethesda III (indeterminate) category, as shown in the table. This is consistent with the known limitations of FNAC in definitively diagnosing thyroid nodules.[8]

The prevalence of TIRADS 3 and 4 ultrasound findings in both malignant and benign groups (53.9% and 46.1%, respectively) is unsurprising, as these categories encompass nodules with uncertain malignant potential . However, the increased prevalence of TIRADS 5 in malignant cases (25.6%) compared to benign cases (6.1%) as seen in the image, further reinforces the opinion that ultrasound is a valuable tool in risk stratification for thyroid nodules.

Our study reveals that the link between serum TSH levels and thyroid malignancy is complex and multifaceted. Recent researches on this topic have provided valuable insight but still further research is required to understand the mechanism of TSH induced carcinogenesis as well as the link between serum TSH levels and thyroid carcinoma progression.

However, it is crucial to acknowledge the limitations of our study. The cross-sectional design precludes establishing

causal relationships, and further research is warranted to explore the underlying mechanisms linking TSH and thyroid carcinogenesis. Additionally, our study population might not be entirely representative of the broader Pakistani population, necessitating further investigations in diverse geographical and socioeconomic groups.

Despite these limitations, our research contributes significantly to the growing body of evidence on the TSH-thyroid cancer association. By illuminating this crucial link in the Pakistani context, we pave the way for more targeted screening strategies and potentially life-saving interventions for this population. Future research should delve deeper into the underlying mechanisms, explore potential genetic and environmental risk factors, and assess the efficacy of TSH-based screening programs in Pakistani healthcare settings. Ultimately, our collective efforts can lead to a future where early detection and effective treatment minimize the burden of thyroid carcinoma in Pakistan and beyond.

CONCLUSION:

The implications of our study extend beyond the realms of clinical research to encompass public health initiatives and healthcare policy formulation. The potential association between elevated TSH levels and thyroid carcinoma diagnosis underscores the imperative of integrating TSH assessment into routine screening protocols for thyroid disorders, particularly in regions with a high burden of thyroid cancer such as Pakistan.

Furthermore, our study underscores the importance of addressing modifiable risk factors contributing to TSH dysregulation and thyroid cancer susceptibility. Public health initiatives aimed at promoting iodine sufficiency, mitigating environmental pollutants, and fostering healthy lifestyle behaviors can potentially attenuate the incidence of thyroid disorders and alleviate the burden of thyroid cancer within the Pakistani populace.

Authors Contribution:
Tehmina Junaid: Conceived and designed the study
Areej Fatimah Iqrar Siddiqui: Conceived and designed the study, wrote the paper
Tariq Zahid Khan: Supervised the study
Zeba Ahmed: Supervised the study
Basit Arif: Data collection
Sana Kazmi: Wrote the paper
Muhammad Umair Tahseen: Data Analysis

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