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Original Article

# Assessment of CA 19-9 in Patients with Thyroid Malignancies

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## Abstract:

Background: Carbohydrate antigen 19-9 (CA 19-9) is a cell surface glycoprotein complex that is used as a tumor marker for pancreatic and biliary malignancies. Its significance in thyroid cancer is controversy. However some studies demonstrated that CA19-9 is expressed in both differentiated and anaplastic thyroid carcinomas.
Objectives: 1.The aim of this work was to investigate the relationship between levels of CA 19-9 and thyroid malignancies and the relation between CA19-9 and prognosis of the disease.
Methods: This case-control study was carried out on 120 subjects; 40 healthy individuals as control (Group I), 40 patients with localized thyroid cancer (Group II) and 40 patients with metastatic thyroid cancer (Group III). CA19.9 was measured in all patients.
Results: Ca19-9 shows significant increase in group II, III as compared to group I (P <0.001). There is significant increase in medullary and follicular thyroid cancer in group III as compared to group II (P= 0.002). The CA19-9 had a cut off (>11.1); showed 87.5% sensitivity, 100% specificity and 97.4% accuracy.

Conclusions: Elevation of CA19-9 with thyroid malignancy is a sign of bad prognosis which requires special care of diagnosis and treatment to be capable of overcoming the serious illness.

**Keywords:** CA 19-9, Thyroid Malignancies, Medullary Thyroid Carcinoma, Papillary Carcinoma, Follicular Carcinoma
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## Introduction:

Thyroid cancer represents about 3.8% of all new cancer cases .(1) Incidence of thyroid cancer in North Africa represents about 2.8% of all new cancer cases with mortality rate about 0.73%.(2)

Thyroid malignancies are classified according to histopathological features into 5 main groups as follows: 1.papillary thyroid carcinoma(PTC): the most common type of thyroid cancer form about 80-90% of all thyroid cancers, 2.follicular thyroid carcinoma forms about 10-15%, 3.anaplastic thyroid carcinoma: is a rare type forms less than 2%, 4. medullary thyroid carcinoma(MTC) forms about 5-10% and 5.few very rare types including lymphoma, and sarcoma.(3)

The WHO Classification of Endocrine and Neuroendocrine Tumors, Fifth Edition, is a publication that includes relevant revisions to the nomenclature, grading, and prognostication of endocrine tumors based on pathologic characteristics and molecular profile ,Table (1). (4)

**Table (1):Follicular cell derived neoplasms of the 2022 World Health Organization classification of thyroid tumors (4)**

| Benign tumors | Low-risk neoplasms | Malignant neoplasms |
|---|---|---|
| -Follicular nodual disease<br>-Follicular adenoma<br>-Follicular with papillary architecture adenoma<br>-Oncocytic adenoma | -Non -invasive follicular thyroid neoplasm with papillary-like nuclear characteristics (NIFTP)<br>- Thyroid follicular tumor of uncertain malignant potential(FT-UMP)<br>-Thyriod well-differentiated tumor of uncertain malignant potential(WD-UMP)<br>-Hyalinizing trabecular tumor( HTT) | - PTC<br>- Follicular thyroid carcinoma (FTC)<br>-Oncocytic carcinoma of the thyroid (OCA)<br>- Invasive encapsulated follicular variant papillary carcinoma (IEFVPTC).<br>-High-grade follicular cell-derived non anaplastic thyroid carcinoma<br>-Poorly differentiated thyroid carcinoma( PDTC)<br>-Anaplastic thyroid carcinoma |

Thyroglobulin (Tg) is a tumour marker for PTC, and is useful for monitoring recurrence in patients who have undergone total thyroidectomy. However, Tg is not a specific marker for PTC because serum Tg levels are elevated even in adenomatous goiters and follicular tumors.(5)

Another thyroid tumour marker is calcitonin and it is the classic tumor marker for MTC. (6) The need for tumour marker that is more sensitive and more specific for thyroid cancer was searched for a long time. Elevated serum level of CA19-9 was observed in patients with PTC with tracheal invasion and is expressed on the cytoplasmic membrane of cancer cells .(5) also in aggressive cases of MTC.(6) and in few patients with anaplastic thyroid carcinoma.(7)

CA19-9 is a glycoprotein that provides adhesion in tissues and may be increased with cell cycle and cell destruction are increased. They are also thought to be secreted from inflammatory tissues.(8) CA19.9 is one of the putative cancer antigens that is quantified worldwide when suspecting gastrointestinal malignancies .(9) CA19-9 was originally described as a gastrointestinal system and pancreas specific tumor marker. (7) CA19.9 could predict mortality in MTC, however serum creatinine and carcinoembryonic antigen levels that were previously assessed were not important markers in MTC, but CA19.9 was significantly associated with progressive disease. (10)

## Patients and Methods:

This study was carried in the Oncology Clinic of Sohag Oncology Center in the period from January 2022 to June 2023, on 120 (40 patients with localized thyroid cancer, 40 patients with metastatic thyroid cancer and 40 healthy individuals as control group), their age and sex matched were matched. The study was done after approval from the Ethical Committee Sohag University Hospitals, Sohag, Egypt. An informed written consent was obtained from the patients.

Inclusion criteria were adult patients newly diagnosed as thyroid carcinoma by histopathological examination.

Exclusion criteria were: patients with benign thyroid tumors, colorectal cancer, pancreatic cancer, pancreatitis, and pregnant female patients.

Patients were classified into three equal groups: **Group I:** Healthy control individuals, **Group II**:

Individuals with localized thyroid malignancy, and **Group III**: Individuals with metastatic thyroid malignancy.

All patients were subjected to complete history taking, clinical examination, histopathological examination of biopsies taken from suspected cases , laboratory investigations [complete blood count (CBC), liver and renal function tests, TSH, Free T3 and T4] and assessment of CA 19-9 levels in patients' serum was assessed.

Blood samples were taken from patients and control subjects as following; 5 ml venous blood was collected by clean venipuncture of 1mL in EDTA tube for CBC and 4 mL in 2 plain tubes .Then centrifugation of the sample for 10 minutes at 3000 RPM to separate serum for kidney ,liver and thyroid function tests and CA 19-9 was done.

**CBC** was performed in Sysmex XN350, automated cell counter, Sysmex Egypt LLC.

Renal and Liver function tests were done on auto-analyzer AU480 (Beckman coulter). Thyroid function tests were done on auto-analyzer ACCESS II (Beckman coulter).

**CA19.9:** this test was done on Beckman coulter, access immunoassay (chemileuminesnce immunoassay). Normal range is 1.98-25.12 U/mL for males and 2.36-29.29 U/mL for females.

**Statistical analysis**

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean ± standard deviation (SD) and compared between the three groups utilizing ANOVA (F) test with post hoc test (Tukey). Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test.

The area under the curve (AUC) evaluates the overall test performance. A two tailed p value < 0.05 was considered statistically significant.

## Results:

Demographic data and laboratory findings of the studied groups were demonstrated in Table 2

**Table 2: Laboratory investigations of the studied groups**

| parameter | | Group I | Group II | Group III | P value |
|---|---|---|---|---|---|
| Age (years) | | 45.100± 16.973 | 51.875±14.002 | 50.225±17.309 | 0.153 |
| Sex | **Male** | 15 | 7 | 8 | 0.079 |
| | **Female** | 25 | 33 | 32 | |
| CBC | **WBC** | 6.974±1.895 | 6.695±2.035 | 7.015±2.072 | 0.740 |
| | **RBC** | 5.052±0.421 | 4.493±0.398 | 4.658±0.587 | **<0.001*** |
| | **HGB** | 14.153±1.426 | 12.063±1.625 | 12.390±1.668 | **<0.001*** |
| | **HCT** | 42.633±3.238 | 36.288±4.532 | 37.418±4.752 | **<0.001*** |
| | **MCV** | 84.575±3.213 | 81.078±6.178 | 80.675±8.076 | **0.009*** |
| | **MCH** | 28.045±1.634 | 27.133±2.602 | 26.688±2.765 | **0.038*** |
| | **PLT** | 271.825±63.673 | 262.100±66.737 | 261.925±73.817 | 0.759 |
| Liver function Test | **ALT** | 13.940±5.584 | 22.455±15.075 | 21.370±12.958 | **0.003*** |
| | **AST** | 19.160±6.962 | 25.920±15.375 | 22.888±11.566 | **0.041*** |
| | **Total bilirubin** | 0.52±0.223 | 0.62±0.27 | 0.56±0.29 | 0.244 |
| | **Direct bilirubin** | 0.13±0.04 | 0.13±0.05 | 0.134±0.06 | 0.831 |
| | **Total protein** | 7.5±0.9 | 7.2±0.6 | 6.9±0.8 | **0.0001** |
| | **Albumin** | 4.355±0.323 | 4.153±0.320 | 4.108±0.297 | **0.001*** |
| Kidney function Test | **Urea** | 21.800±6.107 | 27.335±9.309 | 25.958±10.629 | **0.017*** |
| | **Creatinine** | 0.72±0.8 | 0.81±0.6 | 0.92 ±1.5 | **0.001*** |
| Thyroid function | **TSH** | 1.968±1.055 | 2.731±2.419 | 3.431±3.376 | **0.034*** |
| | **Free T3** | 2.851±0.692 | 2.832±0.988 | 2.810±1.382 | 0.985 |
| | **Free T4** | 1.358±0.990 | 1.284±1.024 | 1.172±0.569 | 0.639 |

Data are presented as mean ± SD or frequency (%). * Significant p value <0.05, CBC: complete blood count, RBCs: red blood cells count, HCT: hematocrit, Hb: hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, WBCs: White blood cells, PLT: platelets, TSH: thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxin.

Ca19-9 showed significant increase in group II and III as compared to group I (p <0.001) as shown in table 3

**Table 3: Comparison between groups as regard CA19-9**

| | Group I (n=40) | Group II (n=40) | Group III (n=40) | P |
|---|---|---|---|---|
| **CA19.9** | 5.676±2.427 | 18.139±7.966 | 35.185±15.455 | **<0.001*** |

Data are presented as mean ± SD. * significant p value <0.05.

Group II and group III subdivided according to histopathological examination into:

Group (II-a): 16(40%) patients with PTC, group (II-b): 24 (60%) patients with follicular thyroid carcinoma. Group (lll-a): 26 (65%) patients with PTC, group (lll-b): 10 (25%) patients with follicular thyroid carcinoma ,and group (lll-c): 4(10%) patients with MCT

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Figure 1: There is significant increase in CA19-9 in MCT and follicular thyroid cancinoma in group III as compared to group II (p= 0.002).

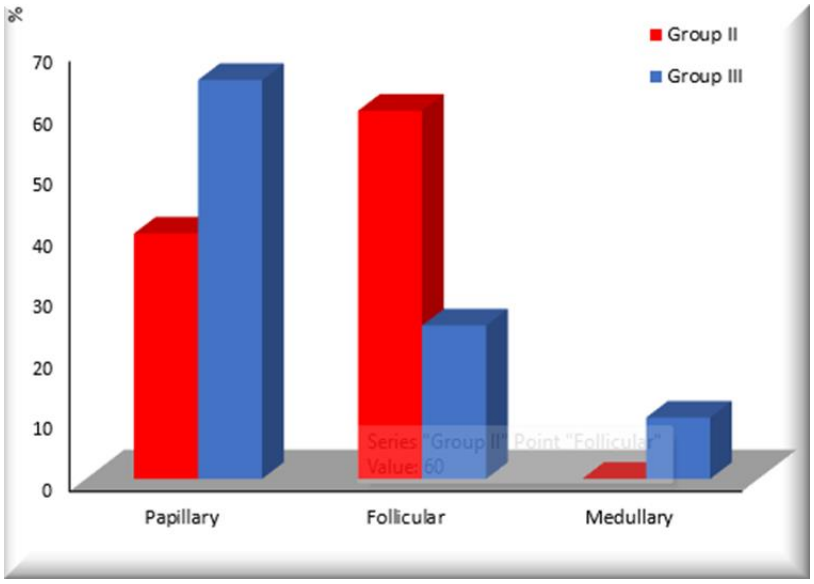


**Figure 1: Comparison between the studied groups as regard to histopathology**

CA19-9 levels show significant increase in group IIb (follicular carcinoma) when compared with group IIa PTC.CA 19-9 levels were significantly increased in group IIIb and group IIIa

. **Table 4**

**Table 4: Comparison of CA19-9 ratio between Group IIa and group IIb and between Group IIIa, group IIIb with group IIIc**

| | Histopathology | N | Mean ±SD | P |
|---|---|---|---|---|
| **Group II** | **Papillary (a)** | 16 | 14.883±5.912 | **0.033*** |
| | **Follicular (b)** | 24 | 20.310±8.515 | |
| **Group III** | **Papillary (a)** | 26 | 33.335±13.061 | **0.022*** |
| | **Follicular (b)** | 10 | 32.098±4.526 | |
| | **Medullary (c)** | 4 | 54.925±32.268 | |

Data are presented as mean ± SD. * Significant p value <0.05.

Microscopic histopathological features of the studied groups were illustrated in figure2,3,and4

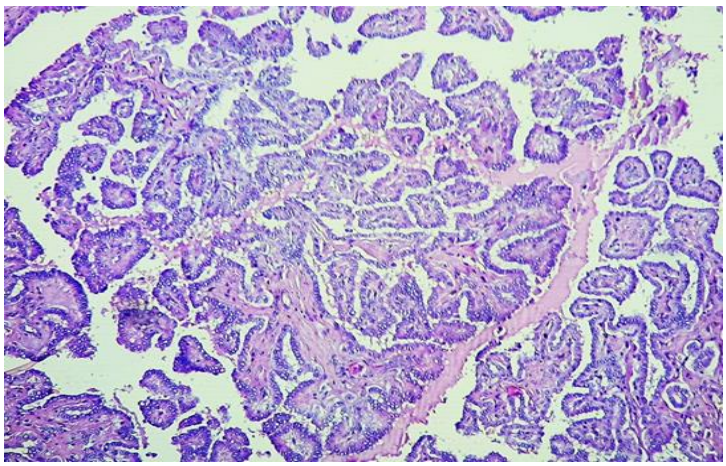

**Figure (2):PTC by light microscopic examination x40 stained with hematoxylin and eosin**

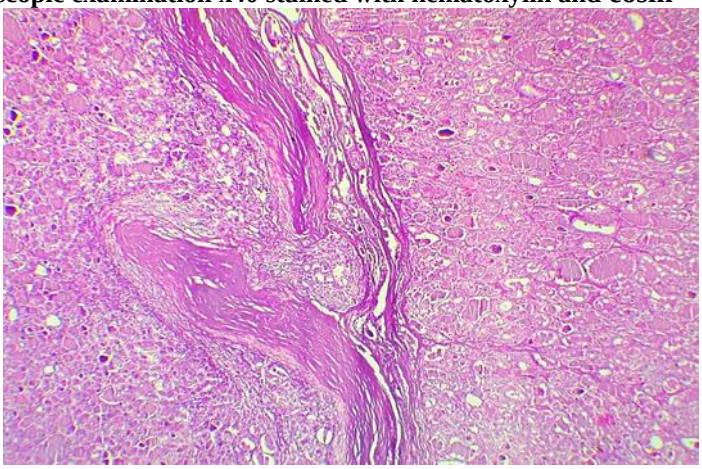

**Figure (3):Follicular thyroid carcinoma examined by light microscopy x100 and stained with hematoxylin and eosin**

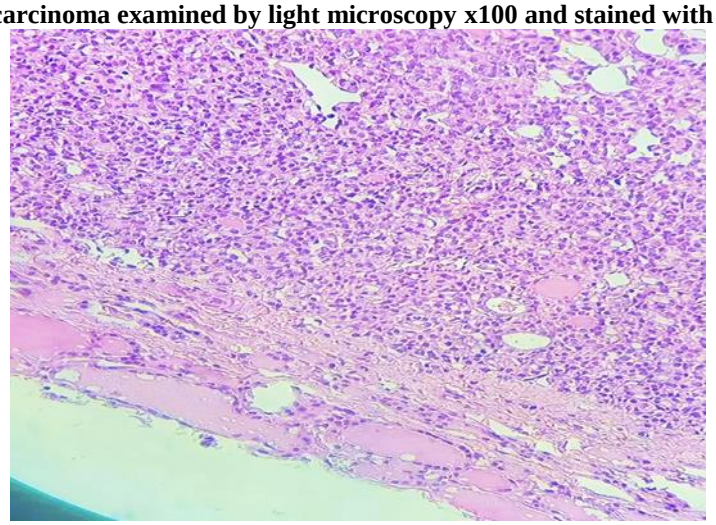

**Figure (4):MTC by light microscopic examination x100 stained with hematoxylin and eosin**

CA19.9 showed no significant correlation with age, WBCS, RBCS, HGB, HCT, MCV, MCH, PLT, ALT, AST, Total bilirubin, Direct bilirubin, Albumin, Creatinine, urea, Uric acid, TSH, Free T3 and Free T4 in Group II and Group III ( Table 5).

**Table 5: Pearson's correlation coefficient study of CA19-9 in group II and group II**

| | CA19.9 | | | |
|---|---|---|---|---|
| | **Group II** | | **Group III** | |
| | r | P-value | r | P-value |
| Age | 0.226 | 0.160 | 0.083 | 0.609 |
| WBC | -0.096 | 0.555 | 0.110 | 0.498 |
| RBC | 0.095 | 0.561 | 0.107 | 0.512 |
| HGB | 0.002 | 0.989 | 0.047 | 0.774 |
| HCT | 0.128 | 0.432 | 0.123 | 0.450 |
| MCV | 0.088 | 0.591 | 0.058 | 0.722 |
| MCH | -0.109 | 0.503 | -0.029 | 0.859 |
| PLT | -0.060 | 0.712 | 0.019 | 0.908 |
| ALT | 0.017 | 0.916 | 0.100 | 0.540 |
| AST | 0.012 | 0.943 | 0.046 | 0.777 |
| Total bilirubin | -0.039 | 0.810 | 0.246 | 0.127 |
| Direct bilirubin | 0.221 | 0.170 | 0.264 | 0.100 |
| Albumin | -0.196 | 0.225 | 0.066 | 0.687 |
| Urea | 0.034 | 0.833 | -0.087 | 0.595 |
| Creatinine | -0.044 | 0.789 | -0.090 | 0.583 |
| TSH | -0.183 | 0.259 | 0.145 | 0.370 |
| Free T3 | 0.199 | 0.219 | -0.166 | 0.306 |
| Free T4 | -0.152 | 0.348 | -0.197 | 0.224 |

r: Pearson coefficient, * Significant p value <0.05, CBC: complete blood count, RBCs: red blood cells count, HCT: hematocrit, Hb: hemoglobin, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, WBCs: White blood cells, PLT: platelets, TSH: thyroid stimulating hormone, T3: Triiodothyronine, T4: Thyroxin.

As regard CA19-9; by comparing group II and group III patients with group I control subjects with cut off result (>11.1). Sensitivity of the test was (87.5%), specificity (100%), PPV was (100%), NPV was (80%) and accuracy of the test was (97.4%) Table(6),Figure(5)

**Table(6):ROC curve between the studied cases and control**

| | **Cutoff** | **Sens.** | **Spec.** | **PPV** | **NPV** | **Accuracy** |
|---|---|---|---|---|---|---|
| **CA19-9** | >11.1 | 87.5 | 100.0 | 100.0 | 80.0 | **97.4%** |

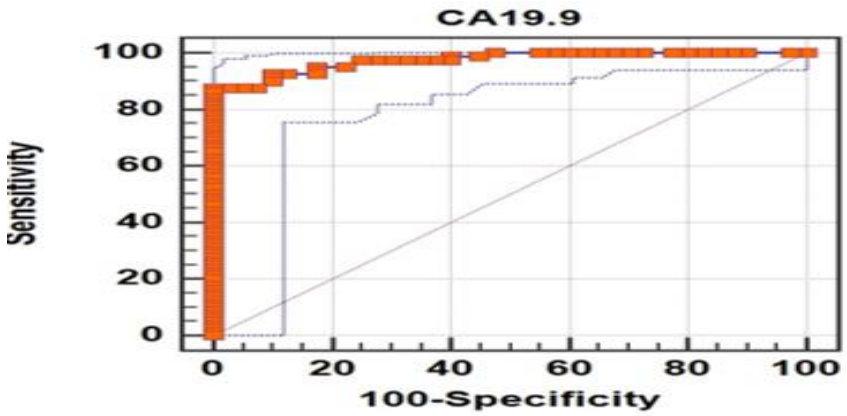


**Figure (5): ROC curve between the studied cases and control**

## Discussion

Thyroid cancer (TC) is the most common malignancy of the endocrine system in 2022.TC represents about 4.1% of all cancer diagnoses worldwide and generally has a good prognosis with a five-year survival rate of about 98.5%. [11]

Its incidence has increased over the years, from 1.5% before 1996 to 6.8% after 1996, with an increase of three times per decade .This increase in incidence has been attributed to a higher diagnosis rate, due to the implementation of imaging techniques (diagnosis achieved in 50% of cases), in addition to genetic and environmental factors, such as obesity and the increase in iodine consumption. [9]

CA 19-9 is a sialylated Lewis (Lewis ab) blood group antigen, synthesized in normal pancreatic parenchyma and biliary tract as well as epithelial cells of the gastric, colonic and uterine mucosa. CA 19-9 is the most used biomarker for PDAC but is also found elevated in other malignancies

such as gastric, colorectal, lung and thyroid cancers. [12] In this study CA19.9 was assessed and its relation with progression of the disease in thyroid cancer patients.

In this study CA19-9 showed significant elevation in whole studied patients when compared to control subjects. Vrbikova J. [7] reported that serum levels of CA19-9 could be increased in differentiated thyroid cancer and could lead to a false suspicion of GIT tumors.

Another study approved that elevated serum CA 19-9 levels and staining of CA 19-9 in neoplastic thyroid conditions, such as anaplastic thyroid carcinoma, anaplastic transformation from papillary carcinoma and papillary carcinoma, have also been reported. On the other side, not all patients with thyroid cancers have been found to express CA 19-9 in the tumor tissue. [13] CA19-9 showed significant increase in group III patients when compared to group I.

This was approved by Alencar R et al. [6] with a study on 122 patients with thyroid malignancies, 48 had distant metastases, and at the end of follow-up 18.1% had persistent disease and 32.7% had progressive disease. CA19-9 was significantly higher in those who had disease progression than in those who had not and was also higher in patients who died from MTC. Kihara M et al.[14] reported a case with high serum CA19-9 diagnosed as liver metastasis from papillary thyroid carcinoma, and paraffin-embedded specimen, was positive for CA19-9 by immunostaining. After thyroidectomy, his serum CA19-9 level markedly decreased. From histopathological point of view, in this study MTC showed the highest levels of CA19-9 when compared to papillary and follicular types. Alencar R et al. [6] found that CA19-9 have a role as a prognostic factor in metastatic MTC.

Another study was done on seven cases presented with MTC showed elevation of CA 19-9 serum levels (average level: 145 IU/l and normal range: <37 IU/l), without any clinical findings of gastrointestinal cancer or inflammation and the immunostaining of the MTC tissue showed strongly positive staining for CA 19-9 .[15]

Additionally, prospective data identify CA 19.9 positivity and fast CA 19.9 serum doubling time (i.e., <6 months) in advanced MTC as independent predictors of mortality, regardless of imaging findings. In these patients, systemic treatment (e.g., with cabozantinib or vandetanib) may be considered sooner than imaging alone would indicate.[10]

However, Jaber T et a.l.[16] linked positive serum Ca19.9 with prediction of mortality but not for progressive disease in patients with advanced MTC.

Giovanella et al.[17] stated that CA 19.9 could not replace established MTC biomarkers (i.e., CT and CEA) but may serve as a useful adjunct in select CA 19.9-positive cases. Its elevation and rapid doubling convey increased mortality risk and may prompt earlier therapeutic intervention independent of imaging findings.

Many studies have shown that an increase in the expression of sialylated glycans, such as CA 19-9, promotes tumor metastasis through increased binding of circulating tumor cells to E-selectin on endothelial cells. A study reported that the expression of CA 19–9 in mice resulted in severe pancreatitis, due to the hyperactivation of epidermal growth factor receptor (EGFR) signaling.[18]Furthermore, CA 19–9 can cooperate with the KrasG12D oncogene to produce aggressive PDAC. Another study demonstrated the immunosuppressive behaviour of CA19–9 for its ability to lead to T-cell apoptosis. Therefore, with its important roles in cancer initiation and progression, CA 19–9 is an attractive target for cancer diagnosis, prognosis, and Therapy. [19]

Limitations of this study included that sample size was relatively small. The study was in a single center. So, we recommended that CA19-9 to be used in screening of thyroid malignant patients and to predict prognosis. Establishing a linked database to document new thyroid cancer cases, follow up current cases.

## Conclusions:

Thyroid malignancies cause marked alterations in levels of CA19-9. Metastatic thyroid malignancies showed a higher increase in CA19-9 levels. MTC shows a higher increase in CA 19-9 among other histopathological types. Elevation of CA19-9 with thyroid malignancy is a sign of bad prognosis that require special effort for diagnosis and treatment to be capable of overcoming this serious illness is recommended.

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**Conflict of Interest:** Nil

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