INTERNATIONAL JOURNAL OF
MEDICAL BIOCHEMISTRY

DOI: 10.14744/ijmb.2020.46220
Int J Med Biochem 2021;4(1):8-13

Research Article

# Evaluation of tumor marker test requests in a hospital setting

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## Abstract

**Objectives:** Early diagnosis and treatment of oncological disease is extremely important and tumor marker tests are a valuable tool; however, requests for testing should not be used in excess or without sufficient cause. The aim of this study was to analyze and evaluate the appropriateness of requests for tumor marker tests at a single hospital.

**Methods:** Tumor marker tests for carcinoembryonic antigen (CEA), cancer antigen (CA) 15-3, CA 19-9, and CA 125 performed by a single biochemistry laboratory between January 1, 2018 and December 31, 2019 were assessed retrospectively. These tumor markers can be used for screening, diagnostic confirmation, estimating prognosis, and monitoring for recurrence. The departments of internal medicine, gastroenterology, endocrine diseases, chest diseases, general surgery, gynecology and obstetrics, and medical oncology were the most common sources of the requests.

**Results:** There were 1420 (40%) requests for CEA, 671 (19%) for CA15-3, 868 (25%) for CA 19-9, and 585 (16%) for CA 125 during the study period. A significant difference based on gender was determined in requests for CEA and CA 125 ($p<0.001$ and $p=0.033$, respectively). In all, 312 (22%) of requests for CEA markers, 202 (30.1%) for CA 15-3, 204 (23.5%) for CA 19-9, and 113 (19.3%) for CA 125 requests were above the reference range. Significant positive correlations were determined between age and CEA, CA 15-3, and CA 19-9 tumor markers ($r=0.262$, $p<0.001$; $r=0.096$, $p=0.013$; $r=0.090$, $p=0.008$, respectively). The preliminary diagnoses supporting the requests included non-specific pain, acute vaginitis, anemia, anxiety disorder, dyspepsia, neoplasia, and thyroid disorder.

**Conclusion:** The results of this study suggest that outpatient clinics made an excessive number of tumor marker requests inconsistent with the preliminary diagnosis. Overutilization of laboratory testing incurs significant costs and affects workload, and may also have other potentially adverse effects on patient care.

**Keywords:** Carcinoembriogenic antigen, oncology, test request, tumor follow-up, tumor markers

Laboratory tests are very important in the diagnosis and follow-up of disease; test results have been reported to contribute as much as 70% to the diagnosis [1]. The use of laboratory testing has increased as a result of new technology decreasing result times [2]. In many countries, growing hospital expenses have had a significant effect on the national budget, and health expenses are predicted to exceed economic growth in some instances [3, 4]. The critical effectiveness of laboratory analysis in the diagnosis and treatment of diseases continues to increase with advancing technology and understanding of molecular developments and new biomarkers. However, in the face of an increasing patient load, laboratory managers often struggle to meet the demand for more tests with faster results while maintaining quality and optimal interpretation [4]. The main target of healthcare should be providing the best possible care for patients. A full test report that does not benefit the patient adds unnecessary detail and economic load. The American Institute of Medicine summarized 21st century health policy aims as providing protective, effective, patient-oriented, equal, efficient, and timely service [5].

Tumor markers are biochemical parameters released either by the tumor tissue itself or as a result of a metabolic change caused by the tumor tissue that can be detected in body fluids. These measured values may be indicative of a malignant cancerous formation, but malignancy is not always the precise cause. These findings can also be the result of non-cancerous conditions, such as inflammation or infection. Tumor markers

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**Submitted Date:** July 26, 2020 **Accepted Date:** September 09, 2020 **Available Online Date:** December 02, 2020

are synthesized from tumor tissues in much larger amounts than normal cells. Generally, these substances are proteins. While they can be found in blood, urine, stool, tumor tissue, or other body fluids, changes in DNA and gene expressions are also now being used as tumor markers [6]. Some markers indicate only 1 cancer, while others can indicate 2 or more cancers. No tumor marker alone is diagnostic.

As with all diagnostic tests, tumor markers are used to evaluate a suspicious condition. These markers can also be used in risk screening and as a tool for early diagnosis [7, 8].

The principal aim of this study was to evaluate the use of tumor markers in a single hospital environment and assess potential overuse.

## Materials and Methods

Approval for this study was granted by Tokat Gaziosmanpasa University Medical Faculty Clinical Researches Ethics Committee at 26 December 2019 with the number of 19-KAEK-266, The Carcinoembriyonic Antigen (CEA), Carbohydrate Antigen 15-3 (CA 15-3), Carbohydrate Antigen 19-9 (CA 19-9), and Carbohydrate Antigen 125 (CA 125) tests requested from outpatient clinics and hospital services between January 1, 2018 and December 31, 2019 were evaluated retrospectively. The data were obtained from the hospital record system. The distribution of the test requests according to clinic and year, the preliminary diagnosis and consistency of the requests, and the frequency of second test requests were evaluated and analyzed using statistical methods.

The data were expressed as median, 25$^{th}$ percentile and 75$^{th}$ percentile (Interquartile Range; IQR), or frequency and percent. The Kruskal-Wallis test was used to compare continuous non-normally distributed data between groups. For multiple comparisons between paired groups, the Mann Whitney U test and the Bonferroni-correction were used. A chi-squared test was used to compare categorical data between groups. A p value of $<0.05$ was considered significant. IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) software was used for the statistical analysis.

## Results

In this study, 1180 (69.4%) of the requests were made for female patients and 520 (30.6%) for male patients. The 57-77 age group was the largest, comprising 826 (48.6%) patients, followed by 609 (35.8%) in the 36-56 age group. Of the total of 3544 requests, 1420 (40%) were for CEA, 671 (19%) for CA 15-3, 868 (25%) for CA 19-9, and 585 (16%) for CA 125. Among these, the oncology clinic made the largest number of requests at 1028 (60.5%). It was observed that 973 (57.2%) of the requests were made with the preliminary diagnosis of neoplasia. The distribution of quantitative data is summarized in Table 1 and quantitative variables according to gender are illustrated in Table 2.

**Table 1. Distribution of quantitative variables**

| | n | % |
|---|---|---|
| Gender | | |
| Female | 1180 | 69.4 |
| Male | 520 | 30.6 |
| Age (Years) | | |
| 15-35 | 126 | 7.4 |
| 36-56 | 609 | 35.8 |
| 57-77 | 826 | 48.6 |
| Over 78 | 139 | 8.2 |
| CEA (ng/mL) | | |
| Negative | 1108 | 78.0 |
| Positive | 312 | 22.0 |
| CA 15-3 (U/mL) | | |
| Negative | 469 | 69.9 |
| Positive | 202 | 30.1 |
| CA 19-9 (U/mL) | | |
| Negative | 664 | 76.5 |
| Positive | 204 | 23.5 |
| CA-125 (U/mL) | | |
| Negative | 472 | 80.7 |
| Positive | 113 | 19.3 |
| Clinics | | |
| Surgical oncology | 13 | 0.8 |
| Endocrinology | 45 | 2.6 |
| Gastroenterology | 94 | 5.5 |
| General surgery | 46 | 2.7 |
| Pulmonary diseases | 3 | 0.2 |
| Internal diseases | 170 | 10.0 |
| Obstetrics and gynecology | 259 | 15.2 |
| Oncology | 1028 | 60.5 |
| Radiation oncology | 11 | 0.6 |
| Diagnosis | | |
| Pain | 129 | 7.6 |
| Acute vaginitis | 8 | 0.5 |
| Anemia | 17 | 1.0 |
| Anxiety disorders | 6 | 0.4 |
| Nausea and vomiting | 5 | 0.3 |
| Dispepsia | 85 | 5.0 |
| Diabetes mellitus | 8 | 0.5 |
| Metromenorrhagia | 94 | 5.5 |
| Endometriosis | 7 | 0.4 |
| Essential hypertension | 21 | 1.2 |
| Gastritis | 16 | 0.9 |
| Verified pregnancy | 2 | 0.1 |
| Angina | 3 | 0.2 |
| Interstitial cystitits | 3 | 0.2 |
| Intervertebral disc herniation | 3 | 0.2 |
| Female infertility | 3 | 0.2 |
| Chronic viral hepatitis | 4 | 0.2 |
| Unspecified mass of the breast | 18 | 1.1 |
| Other non-specified reasons | 53 | 3.1 |
| Neoplasia | 973 | 57.2 |
| Pelvic and perineal pain | 138 | 8.1 |
| Pneumonia | 4 | 0.2 |
| Thyroid gland disorders | 18 | 1.1 |
| Vitamin D deficiency | 51 | 3.0 |

CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

**Table 2. Distribution of quantitative variables by genders**

| | Gender | | |
|---|---|---|---|
| | Female n (%) | Male n (%) | p |
| Age (years) | | | |
| 15-35 | 115 (9.7) | 11 (2.1) | <0.001 |
| 36-56 | 485 (41.1) | 124 (23.8) | |
| 57-77 | 502 (42.5) | 324 (62.3) | |
| Over 78 | 78 (6.6) | 61 (11.7) | |
| CEA (ng/mL) | | | |
| Negative | 766 (83.3) | 342 (68.4) | <0.001 |
| Positive | 154 (16.7) | 158 (31.6) | |
| CA 15-3 (U/mL) | | | |
| Negative | 444 (69.6) | 25 (75.8) | 0.452 |
| Positive | 194 (30.4) | 8 (24.2) | |
| CA 19-9 (U/mL) | | | |
| Negative | 333 (78.7) | 353 (79.3) | 0.827 |
| Positive | 90 (21.3) | 92 (20.7) | |
| CA 125 (U/mL) | | | |
| Negative | 468 (83.3) | 14 (60.9) | 0.006 |
| Positive | 94 (16.7) | 9 (39.1) | |

Chi-squared test. CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

A weak positive correlation was seen between age and CEA requests, and a negligibly positive correlation with CA 15-3, CA 19-9, and CA 125. Also, a weak positive correlation was determined between CEA and CA 15-3, and between CA 19-9 and CA 125. There was also a weak positive relationship between CA 15-3 and CA 125. Lastly, a weak positive relationship between CA 19-9 and CA 125 was identified. The distribution of quantitative variables by age intervals is provided in Table 3. Tables 4 and 5 show the distribution of qualitative variables by gender and age group.

## Discussion

There is no definitive marker for the diagnosis of a tumor in either the healthy population or a high-risk group. Many tumor markers are used as potential cancer screening tools despite their low sensitivity and specificity, however, tumor marker screening has not been shown to reduce cancer-related mortality [9].

Determining the tissue origin of unknown primary tumors is one of the important areas for tissue-specific tumor marker analysis. CA 125 for ovarian cancer and CA 15-3 for breast cancer are the most frequently used. CA 125 is recommended for a benign/malignant differential diagnosis of pelvic masses in post-menopausal women. Consultation with a gynecologic oncologist is recommended in pre-menopausal women admitted with a pelvic mass and a CA 125 value of >200 U/L [10].

Estimating prognosis is another area of tumor marker use in oncology. Determining the difference between a prognostic and a predictive factor is an important consideration. The prognostic factor is associated with the tumor's risk of invasion and metastasis, regardless of treatment [11].

In addition to clinical and radiological procedures, serum tumor markers are also frequently used in the follow-up of solid tumors [12]. The CEA level can determine recurrent/metastatic colorectal cancer with approximately 80% sensitivity and 70% specificity, according to several meta-analyses [13]. In ovarian and breast cancer, CA 125 and CA 15-3, respectively, are commonly used in follow-up, yet for breast cancer, a survival advantage in terms of recurrence has not

**Table 3. Distribution of quantitative variables by age interval**

| | Age intervals | | | | |
|---|---|---|---|---|---|
| | 15-35 n (%) | 36-56 n (%) | 57-77 n (%) | Over 78 n (%) | p* |
| CEA (ng/mL) | | | | | |
| Negative | 56 (100) | 396 (84.1) | 567 (74.1) | 89 (69.5) | <0.001 |
| Positive | 0 (0) | 75 (15.9) | 198 (25.9) | 39 (30.5) | |
| CA 15-3 (U/mL) | | | | | |
| Negative | 32 (86.5) | 200 (71.2) | 204 (67.1) | 33 (67.3) | 0.096 |
| Positive | 5 (13.5) | 81 (28.8) | 100 (32.9) | 16 (32.7) | |
| CA 19-9 (U/mL) | | | | | |
| Negative | 33 (89.2) | 188 (80.3) | 390 (78.8) | 75 (73.5) | 0.219 |
| Positive | 4 (10.8) | 46 (19.7) | 105 (21.2) | 27 (26.5) | |
| CA 125 (U/mL) | | | | | |
| Negative | 87 (88.8) | 231 (88.2) | 140 (75.3) | 24 (61.5) | <0.001 |
| Positive | 11 (11.2) | 31 (11.8) | 46 (24.7) | 15 (38.5) | |

p*: Chi-squared test. CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

**Table 4. Distribution of qualitative variables by gender**

| | Gender | | |
|---|---|---|---|
| | **Female** | **Male** | **p*** |
| Age (years) | 56 [46-67] | 64 [56-72] | <0.001 |
| CEA (ng/mL) | 2.01 [1.25-3.59] | 3.08 [1.87-6.8] | <0.001 |
| CA15-3 (U/mL) | 18.66 [12.95-26.37] | 18.33 [11.58-24.84] | 0.631 |
| CA 19-9 (U/mL) | 14.26 [7-31.92] | 12.91 [7.3-31.59] | 0.736 |
| CA125 (U/mL) | 14.86 [10.07-24.84] | 23.74 [13.86-109.1] | 0.033 |

p*: Mann-Whitney U test; data are presented with median and Interquartile range (IQR) values.CEA: Carcinoembryonic antigen, CA: Carbohydrate antigen

been demonstrated based on tumor markers. In cases considered to be disease-free, monitoring of occult metastases is generally only recommended for germ-cell tumors and colorectal cancer [14, 15].

The evaluation of the usefulness of a tumor marker is directly related to probability and likelihood ratios [16]. If a disease has a high prevalence in the community and there is an effective treatment for this disease, a marker that specifically reveals that disease is the most beneficial. Specificity value assesses the ability of a marker to correctly determine true negative rate in benign cases of a particular disease [17]. Numerous studies have highlighted the effectiveness of tumor markers in oncological conditions.

Saatli et al. [18] reported that many scoring systems using several tumor markers have been developed for the pre-operative benign/malignant differentiation of pelvic masses. There is no single marker that can diagnose ovarian cancer, however, the most specific and sensitive known marker is CA 125, and when measurements are combined with the results of a pelvic examination, pelvic ultrasonography, and menopause status, the accuracy rate increases.

Bast et al. [19] first reported in the 1980s that the serum CA 125 level increased in non-mucinous epithelial ovarian cancer, and the preoperative serum CA 125 level is still used in the differential diagnosis of benign/malignant masses.

Van Gorp et al. [20], in their 2011 study, analyzed 374 patients. Of these, 224 (59.9%) were cases of a benign pelvic mass and 150 (40.1%) were malignant. The patients with a benign mass (mean age: 46.2 years [IQR: 44.1-48.3 years]) were younger than those with malignant tumors (mean age: 57.7 years [IQR: 55.7-59.8 years]) (p<0.001).

According to an analysis of histopathological diagnoses reported by Şahin et al. [21], 14 of 103 patients had malignant ovarian tumors, 14 had a non-ovarian malignant tumor, and 75 had a benign pelvic mass. The median age of the 14 patients with a malignant ovarian tumor was 45.3 years, and 57% were postmenopausal. The CA 125 level was normal in 1 of the 14 cases (7.1%) and above 65 U/mL in 13 (92.9%). In the patients with a benign pelvic mass, the median age was 35.7 years and 8% were postmenopausal. The serum CA 125 level was normal in 54 (72%) of 75 cases, and above 35 U/mL in 21 (28%). In our study, it was determined that the CA 125 sensitivity was 92.9% and the specificity was 72%.

Yetimalar et al. [22] found that in 48 patients between 20 and 72 years of age the mean CA 125 level for the malignant tumor group was 427.5 U/mL and 42.12 U/mL for the benign mass group [19].

In a retrospective study of intracranial epidermoid cyst patients treated between 2009 and 2014 and healthy controls, Wang et al. [23] compared the general serum tumor markers of CA 19-9, CEA, CA 125, and squamous cell carcinoma-associated antigen levels. The CA 19-9 measurement was found to be diagnostic for intracranial epidermoid cyst with a cut-off value of 13.15 U/mL. Tumor size was associated with the CA 19-9 level, but the CA 19-9-positive group did not demonstrate a statistically significant recurrence rate.

Liu et al. [24] found that a tumor marker panel demonstrated excellent diagnostic performance for malignant ascites. Evaluation of tumor markers may represent a beneficial adjunct to cytology for patients who can benefit from further invasive procedures.

Acharya et al. [25] discussed how tumor markers have long been utilized to monitor gastrointestinal cancers. Traditional markers are useful in colorectal cancer surveillance, but in esophagogastric malignancies, the results were somewhat less defined and require clarification.

Ma et al. [26] concluded that a single measurement of CEA, CYFRA 21-1, and CA 125 was of diagnostic value in the diagnosis of lung cancer. Detection of these 3 tumor markers could

**Table 5. Distribution of qualitative variables by age intervals**

| | Age intervals | | | | |
|---|---|---|---|---|---|
| | **15-35** | **36-56** | **57-77** | **Over78** | **p** |
| CEA | 28 [24-32] (a) | 49 [44-53] (b) | 65.5 [61-70] (c) | 80 [79-83] (c) | <0.001 |
| CA 15-3 | 1.46 [0.71-2.07] (a) | 1.9 [1.16-3.53] (b) | 2.69 [1.67-5.3] (b) | 3.03 [1.68-6.22] (b) | 0.003 |
| CA 19-9 | 13.82 [11.57-17.1] | 18.68 [12.7-26.14] | 19.44 [13.82-29.03] | 20.04 [12.98-25.63] | 0.167 |
| CA 125 | 9.59 [7.23-18.04] (a) | 13.57 [5.92-28.78] (a) | 13.7 [7.4-32.15] (a) | 14.4 [8.52-39.1] (b) | 0.001 |

Data were presented with median and Interquartile range (IQR) values. Kruskal Wallis test was used. (abc): The common letter refers statistical insignificance. CEA: Carcinoembryonic antigen, CA:Carbohydrate antigen

greatly improve the sensitivity of a non-small cell lung cancer diagnosis.

Studies in the literature have generally been related to a particular disease and its associated tumor marker. Our study evaluated all of the outpatient clinic tumor marker requests of a hospital. We observed that tumor marker requests were made for 502 (42.5%) female patients and 324 (62.3%) male patients, most often in the 57-77 age group, and a significant difference was found between the 2 groups (p<0.001). This is very useful data for public health specialists who may conduct screening studies focused on a particular group and provide clinicians with more specific age and gender group information.

The CEA, CA 15-3, CA 19-9, and CA 125 results for males and females were positive in 154 (16.7%)/158 (31.6%), 194 (30.4%)/8 (24.2%), 90 (21.3%)/92 (20.7%), and 94 (16.7%)/9 (39.1%), respectively. The relationship of CEA and CA 125 requests to gender was statistically significant (p<0.001 and p=0.006, respectively).

When the marker requests were evaluated in terms of age groups, the CEA level was highest in those over 78 years of age (39, 30.5%), CA 15-3 was highest in those 57-77 (100, 32.9%), CA 19-9 in those over 78 years (27, 26.5%), and CA 19-9 in those over 78 years (15, 38.5%). The relationship between CEA and CA 125 request results and age group was statistically significant (p<0.001 and p<0.001, respectively).

The analysis of female/male ratio and patient age revealed a CEA median of 56 years (IQR: 46-67 years)/64 years (IQR: 56-72 years), 2.01 ng/mL (IQR: 1.25-3.59 ng/mL)/3.08 ng/mL (IQR: 1.87-6.8 ng/mL), and a CA 125 IQR of 14.86 U/mL (Q1-Q3: 10.07-24.84 U/mL)/23.74 U/mL (IQR: 13.86-109.1 U/ mL), respectively. Statistically significant relationships were observed (<0.001, <0.001, and p=0.033, respectively).

In Table 5; the median values of the CEA, CA 15-3, CA 19-9, and CA125 requests compared by age groups of 15-35, 36-56, 57-77 and over 78, respectively. We found them as follow; CEA: 28 ng/mL (IQR: 24-32 ng/mL)/1.46 ng/mL (IQR: 0.71-2.07 ng/mL)/13.82 ng/mL (IQR: 11.57-17.1 ng/mL)/9.59 ng/mL (IQR: 7.23-18.04 ng/mL); CA 15-3: 49 U/mL (IQR: 44-53 U/mL)/1.9 U/mL (IQR: 1.16-3.53 U/mL)/18.68 U/mL (IQR: 12.7-26.14 U/mL)/13.57 U/mL (IQR: 5.92-28.78 U/mL); CA 19-9: 65.5 U/mL (IQR: 61-70 U/mL)/2.69 U/mL (IQR: 1.67-5.3 U/mL)/19.44 U/mL (IQR: 13.82-29.03 U/mL)/13.7 U/mL (IQR: 7.4-32.15 U/mL); and CA 125: 80 U/mL (IQR: 79-83 U/mL)/3.03 U/mL (IQR: 1.68-6.22 U/mL)/20.04 U/mL (IQR: 12.98-25.63 U/mL)/14.4 U/mL (IQR: 8.52-39.1 U/mL). With the exception of the group aged over 78, the median CEA value was similar between age groups (p<0.001). For CA 15-3, the value of the 15-35 age group was significantly different from that of the other age groups (p=0.003). The CA 125 result for the age group over 78 was also significantly different from that of the other age groups (p<0.001).

Overuse of tumor marker tests is a concern in our country and around the world. Evaluation of non-targeted tumor markers can cause anxiety in patients and unnecessary investigation. The primary purpose of assessing these markers should be to provide clear and appropriate information. The need for a tumor marker request should be considered carefully. Doctors should be familiar with the validation processes in use to ensure the accuracy of the reported test results, and laboratory specialists should be able to provide convincing evidence that the results of the laboratory are reliable.

Feedback about results, physician education, changes in laboratory request forms, policies related to laboratory test order, and financial considerations may improve the use of laboratory testing of tumor markers [27].

In our hospital clinics, it appears that laboratory marker testing may be requested without sufficient regard for the specifics of the patient's age, gender, and the preliminary diagnosis. Our study was designed to examine and analyze the requests for tumor marker testing in terms of the clinics that made the requests and the diagnosis on which the requests were based. Although we did not find significant evidence of overuse, our results indicated that various clinics, many of which rarely see patients with a malignant condition, make tumor marker requests that do not necessarily correlate with the preliminary diagnosis.

The test results for CEA, CA15-3, CA 19-9, and CA 125 were negative at a ratio of 78%, 70%, 76%, and 81%, respectively. This suggests that outpatient clinics make requests without targeting a specific diagnosis.

The number of requests varied by clinic specialty. Requests were made with a wide range of diagnosis from angina (0.2%) to neoplasia (57.2%) and a median of 76.25% of the requests yielded a negative result. Most may have been unnecessary.

The rate of the use of tumor marker tests requests based on age, clinic, and diagnosis was similar in our hospital to that of other hospitals throughout our country. The results of our study could provide significant guidance for clinicians to perform more efficient and accurate patient evaluation. The appropriate use of laboratory testing is important for hospitals, public health, and efficient national health services.

## Conclusion

Tumor markers can serve as a clinical guide developed by multidisciplinary groups based on a systematic and critical evaluation of scientific literature. Tumor marker testing should be used for the intended purposes without causing unnecessary work and cost burdens.

**Acknowledgments:** We thank the laboratory staff and information processing unit staff of our hospital for their great contribution to this study.

**Conflict of Interest:** The author states that there is no conflict of interest for this manuscript.

**Ethics Committee Approval:** This study was approved by the clinical research ethics board of Tokat Gaziosmanpasa University Faculty of Medicine (Date: 26.12.2019/Number: 19-KAEK-266).

**Financial Disclosure:** None declared.

**Peer-review:** Externally peer-reviewed.

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