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Research article

Evaluation of CEA, CA125, CA15-3, CA19-9, AFP and PSA Serum Tumor Markers Status and their Association with Gender and Age in a Libyan Population

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Abstract

Background: Serum tumor markers are extensively used for assisting cancer diagnoses, therapeutic monitoring, and prognostication in clinical practice. **Aim:** This study aimed to evaluate the levels of six selected serum tumor markers and their association with gender and age risk factors in a Libyan population. **Methods:** Serum samples were obtained from each individual involved in this study and the level of CEA, CA125, CA15-3, CA19-9, AFP and PSA tumor markers were quantified by an electrochemiluminescence immunoassay analyzer. **Results:** Among the 2072 participants, 18.8% of individuals showed abnormal serum levels of tumor markers and the mean serum levels of all measured tumor markers were higher than their normal ranges used in this study with higher levels of CEA and CA125 were reported in females when compared to males. CEA, CA19-9, PSA and fPSA levels increased with age while AFP levels were high only in the 1st decade of age. On the other hand, CA125 and CA15-3 levels did not vary with age. **Conclusion:** This study has documented the serum levels of six tumor markers and identified significant gender and age differences in their levels in a Libyan population.

Keywords: tumor markers, gender, age, Libya

Introduction

Cancer is becoming the leading cause of death worldwide (Jung *et al*., 2018; Bray *et al*., 2021; Sung *et al*., 2021). Tumor Markers (TMs) are diverse molecules detected in blood in low concentrations and include serum proteins, enzymes, oncofetal antigens, hormones, metabolites and receptors (Jayanthi *et al*., 2017). Cancer patients show high serum levels of these TMs as a result of direct production by the tumor cells or as an effect of the tumor cells on healthy tissues (Trapé *et al*., 2024). Depending on the TM and type of malignancy, they are clinically used in cancer diagnosis, prognosis and screening, but they are of most value in monitoring treatment, assessing long term follow-up and detecting early recurrence (Hayes *et al*., 1996; Perkins *et al*., 2003; Duffy, 2007; Sundaresan *et al*., 2024). The most frequently used serum TMs in clinical practice are Carcinoembryonic Antigen (CEA), Cancer Antigen 125 (CA125), Cancer Antigen 15-3 (CA15-3), Carbohydrate Antigen 19-9 (CA19-9), Alpha1Fetoprotein (AFP) and Prostate Specific Antigen (PSA).

The CEA is an oncofetal glycoprotein, normally expressed in mucosal cells with low level plasma concentration in adults. It is abnormally over-expressed in adenocarcinoma with high plasma concentration, especially in the case of colorectal cancer; although levels also can be increased in other malignancies such as lung, breast, and gastrointestinal tumors (Fletcher, 1986; Bozkurt *et al*., 2013; Deng *et al*., 2015; Cacho-Díaz *et al*., 2019). AFP is also an oncofetal glycoprotein normally synthesized by the fetal liver and shows undetectable serum levels after birth at an age of 7–10 months (Bader *et al*., 2004). Its high serum levels in adults is seen as a result of re-expression in cases of hepatocellular carcinoma and germ cell tumors (Johnson, 2001). CA125 is a glycoprotein normally expressed in the ovary and other tissues of müllerian duct origin (Tuxen *et al*., 1995). CA125 is used in detection of early stages of ovarian cancers and for therapy monitoring (Klug *et al*., 1984; Sundar *et al*., 2015; McCudden & Willis, 2018). However, CA125 serum levels rises in other cancers such as lung and endometrium, as well as physiological conditions such as pregnancy and menstruation (Jacobs & Bast Jr, 1989; Sturgeon *et al*., 2011; Fini *et al*., 2021). CA15-3 is a high molecular trans-membrane adhesion glycoprotein shows high serum levels in breast cancer (Tobias, 1985; Berry *et al*., 1985; Duffy, 2006; Filella *et al*., 2023). CA19-9 is also an adhesion molecule rise in the blood primarily in cases of pancreatic and biliary tract cancers (Koprowski *et al*., 1981; Steinberg, 1990; Duffy, 2012). Elevation of CA19-9 is detected in other malignancies such as colon, ovary, oesophageal and hepatic cancers as well as benign

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conditions such as cirrhosis, cholestasis and pancreatitis (Staab *et al*., 1984; Steinberg, 1990; Kelly *et al*., 2010; Bozkurt *et al*., 2013; Deng *et al*., 2015). PSA is a glycoprotein produced only by prostatic epithelial cells, found in low levels in healthy men as free (fPSA) and complexed forms with α1-antichymotrypsin or α2-macroglobulin and its level is elevated in prostate cancers (Association, 2000; Loeb & Catalona, 2007).

Many risk factors have an impact on the serum levels of tumor biomarkers in individuals to be investigated such as age, gender, geographic location, diet and life Style (Li *et al*., 2021; Chen *et al*., 2024). Although few studies investigated the clinical use of some TMs in breast cancer in Libya (Elfagieh *et al*., 2012; Jarari *et al*., 2018), to the best of the authors' knowledge, there is no literature studies reported the mean values of TMs in Libyan people. Therefore, this study aimed to document the mean levels of selected TMs in a Libyan population and their association with gender and age factors.

Materials and methods

Tumor markers investigation assays

TMs were investigated in Aljourey Laboratory for Medical Investigation, Tripoli, Libya in the period between March 2021 and October 2023 in the sera of 2072 individuals referred from hospital or self-referred. The electrochemiluminescence immunoassay "ECLIA" by a Elecsys cobas e411 analyzer (Roche, USA) was used in the lab to investigate the serum levels of CEA in 463 individuals, CA125 in 158 individuals, CA15-3 in 201 individuals, CA19-9 in 247 individuals, AFP in 110 individuals, PSA in 535 individuals and fPSA in 358 individuals. The serum values of TMs were calculated according to the manufacturer instructions with reference range of CEA (≤5.0ng/mL), CA125 (≤35U/mL), CA15-3 (≤28U/mL), CA19-9 (≤39U/mL), AFP (≤10U/mL), PSA (≤4.4ng/mL) and fPSA (≤1.0ng/mL).

Statistical analysis

For statistical analysis, the effects of gender and age were investigated by grouping the participating individuals into male and female groups; and decade groups. The decade groups were as following: 1st decade (0-10 years), 2nd decade (11-20 years), 3rd decade (21-30 years), 4th decade (31-40 years), 5th decade (41-50 years), 6th decade (51-60 years), 7th decade (61-70 years), 8th decade (71-80 years), 9th decade (81-90 years), and 10th decade (91-100 years).

For gender analysis, the male groups were compared with the female ones while age analysis was performed by comparing each decade group to the other decades combined together in one group.

Results are expressed as mean±SEM and data were analyzed using GraphPad Prism statistical software (version 6.07; GraphPad Software Inc., La Jolla, CA, USA). Analysis of data between groups was performed using Mann Whitney test and statistical significance between groups was accepted at $p<0.05$.

Ethical approval

This study was approved by the Bioethics Committee at the Libyan Center for Biotechnology Research (BEC-BTRC), under the reference No; NBC: 001.H.25.77.

Results

Number (n) and percentage (%) of the study population are shown in table 1. The serum levels of CEA, CA125, CA15-3, CA19-9, AFP, PSA and fPSA TMs were determined in 2072 individuals with age range, in years, from the 1st decade to the 10th decade with the highest numbers of participants were from the 6th decade, with 468 individuals (22.6%), and the lowest numbers from the 1st decade, with only 3 individuals (0.1%). The gender effect was investigated in 1179 individuals with 387 males (32.8%) and 792 females (67.2%). Among the 2072 participants, 81.2% (n=1683) showed normal serum levels of the tested TMs while 18.8% (n=389) showed abnormal levels.

The mean±SEM levels of CEA, CA125, CA15-3, CA19-9 and AFP TMs in the serum of 387 male and 792 female individuals are shown in figure 1. The CEA and CA125 values were significantly higher in the serum of female individuals than the male ones while the CA15-3, CA19-9 and AFP values did not show significant differences between the tested groups.

The mean±SEM levels of CEA, CA125, CA15-3, CA19-9, AFP, PSA and fPSA TMs in the serum of 2072 individuals with different age decades are shown in figure 2. The 1st decade group showed high levels of AFP while the 2nd and 3rd decade groups showed low levels of CEA. The 4th, 5th and 6th decade groups showed low levels of PSA and fPSA while the 7th decade group showed high levels of CEA. The 8th and 9th decade groups showed high levels of PSA, fPSA and CA19-9. However, CEA level was high in the 8th decade group and low in the 9th decade group. No age differences were observed regarding CA125 and CA15-3 TMs.

The mean±SEM levels of CEA, CA125, CA19-9 and AFP TMs in the serum of 387 male and 792 female individuals with different age decades are shown in figure 3. Female groups showed higher CEA levels than males at the 6th and 9th decades and higher CA125 levels at the 7th decade. Males showed higher AFP levels at the 6th decade and high CEA levels at the7th and 8th decades when compared to the female ones. CA19-9 TM did not show significant different levels between the tested groups.

Discussion

Investigation of serum tumor markers is a simple, non-invasive, low cost and fast way used in oncology to provide valuable information for cancer patient management (Filella *et al*., 2023; Sasanpour *et al*., 2024). As little is known about the mean levels of serum TMs in Libyan people, the aim of this study was to evaluate the serum levels of six frequently used TMs and their association with age and sex risk factors in a Libyan population.

CEA levels were higher than the normal range (≤5.0 ng/mL) with mean±SEM of 15.69±6.93 ng/mL. CEA levels were higher in females than males in this study, with mean±SEM of 17.53±10.83 ng/mL and 12.90±5.94 ng/mL for female and male individuals respectively. This finding was inconsistent with Nah *et al*. (2023), who reported higher levels of CEA in males. CEA levels showed an increase with age where it was low at the 2nd

Table 1. Distribution of the study population.

Parameter	Number and percentage; n (%)							
	CEA	CA125	CA15-3	CA19-9	AFP	PSA	fPSA	Total
TM Levels								2072
Normal	398 (85.9)	135 (85.5)	173 (86.1)	204 (82.6)	93 (84.5)	399 (74.6)	281 (78.5)	1683 (81.2)
Abnormal	65 (14.1)	23 (14.5)	28 (13.9)	43 (17.4)	17 (15.5)	136 (25.4)	77 (21.5)	389 (18.8)
Gender								1179
Male	184 (39.7)	23 (14.5)	10 (5)	112 (45.3)	58 (52.7)			387 (32.8)
Females	279 (60.3)	135 (85.5)	191 (95)	135 (54.7)	52 (47.3)			792 (67.2)
Age (years)								2072
1st decade (0-10)					3 (2.7)			3 (0.1)
2nd decade (11-20)	8 (1.7)	2 (1.2)	3 (1.5)	5 (2.1)	9 (8.2)	6 (1.1)		33 (1.6)
3rd decade (21-30)	66 (14.3)	29 (18.3)	19 (9.4)	32 (12.9)	11 (10)	49 (9.2)	20 (5.6)	226 (10.9)
4th decade (31-40)	101 (21.8)	39 (24.9)	56 (27.9)	36 (14.5)	24 (21.8)	53 (9.9)	26 (7.3)	335 (16.2)
5th decade (41-50)	100 (21.6)	41 (25.9)	47 (23.4)	42 (17)	15 (13.6)	60 (11.3)	45 (12.6)	350 (16.9)
6th decade (51-60)	86 (18.6)	26 (16.4)	43 (21.4)	64 (25.9)	25 (22.7)	138 (25.8)	86 (24.1)	468 (22.6)
7th decade (61-70)	59 (12.7)	12 (7.6)	23 (11.4)	33 (13.4)	10 (9.1)	113 (21.1)	88 (24.6)	338 (16.3)
8th decade (71-80)	31 (6.7)	9 (5.7)	7 (3.5)	25 (10.1)	8 (7.2)	87 (16.2)	74 (20.6)	241 (11.6)
9th decade (81-90)	10 (2.2)		3 (1.5)	10 (4.1)	5 (4.5)	23 (4.3)	17 (4.7)	68 (3.3)
10th decade (91-100)	2 (0.4)					6 (1.1)	2 (0.5)	10 (0.5)

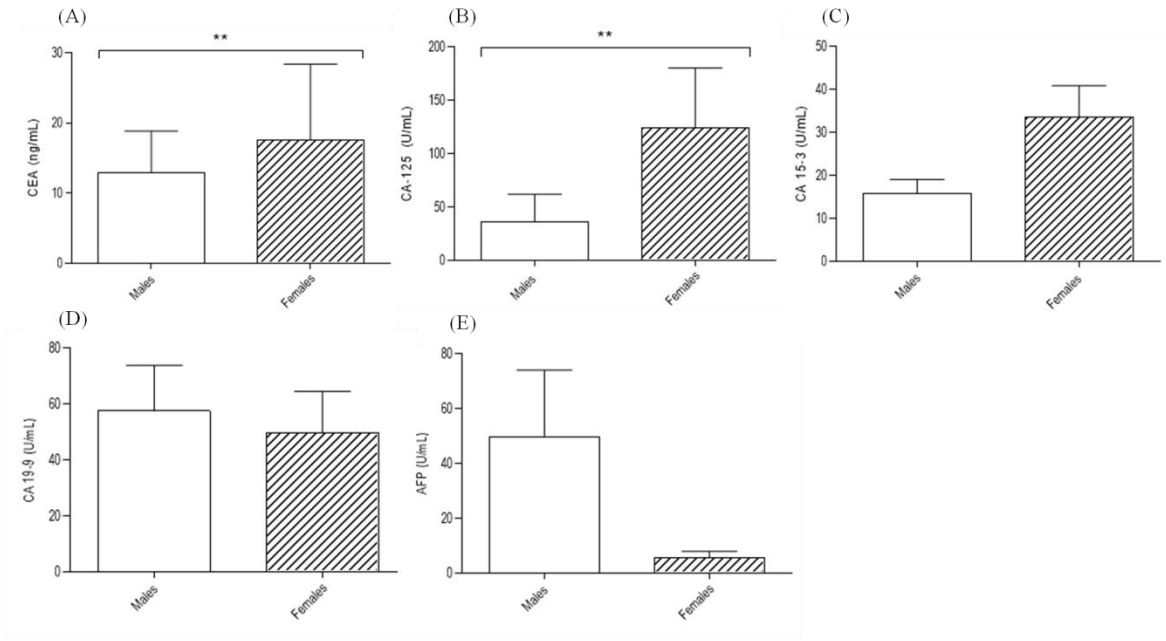


Figure 1. Tumor markers association with gender. The serum levels of CEA (A), CA125 (B), CA15-3 (C), CA19-9 (D) and AFP (E) TMs were compared between males and females of 1179 individuals. Values are expressed as mean±SEM of 184 males and 279 females (CEA), 23 males and 135 females (CA125), 10 males and 191 females (CA15-3), 112 males and 135 females (CA19-9), 58 males and 52 females (AFP) and were compared using Mann–Whitney test with **representing p≤0.01.

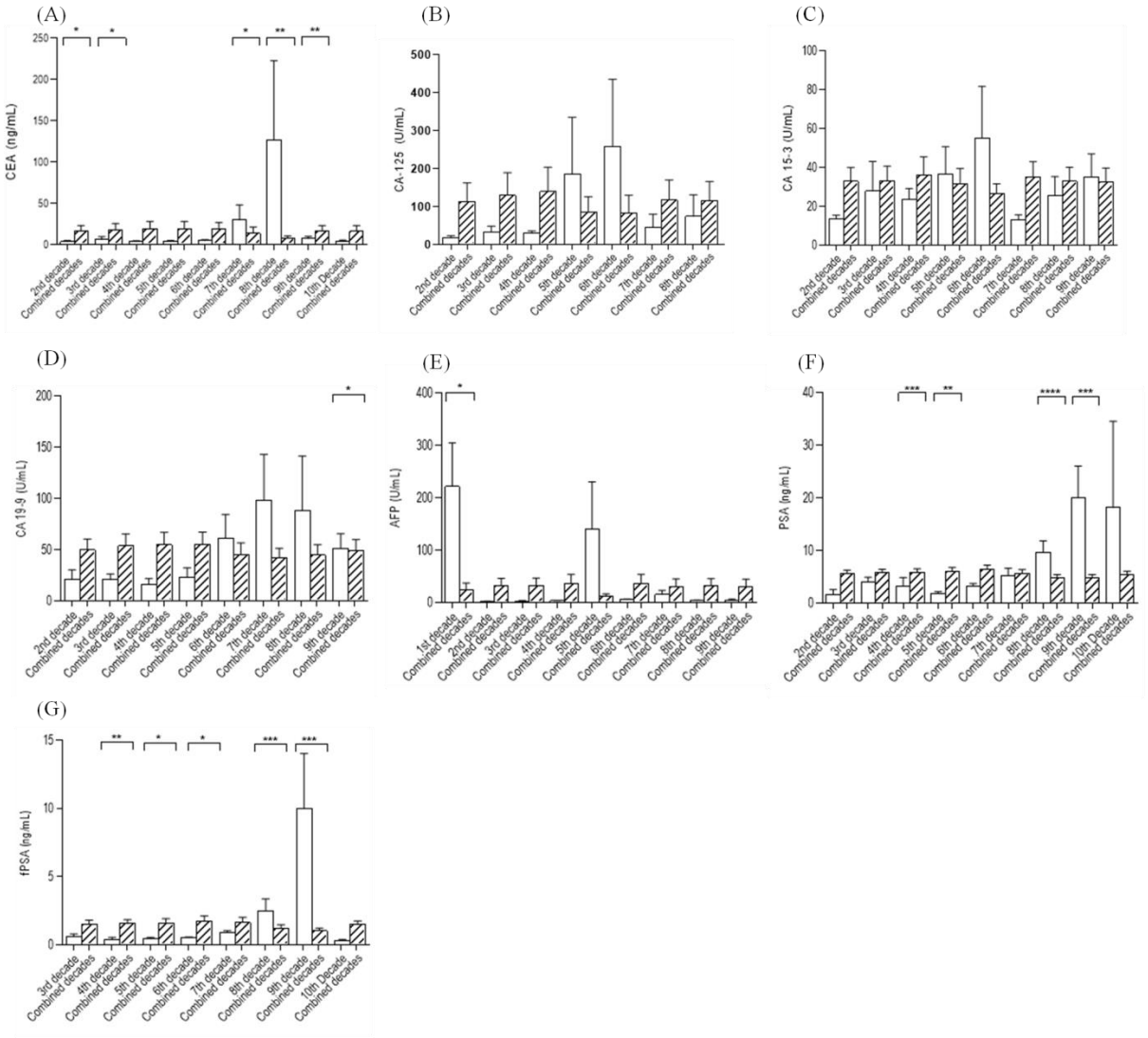


Figure 2. Tumor markers association with age. The serum levels of CEA (A), CA125 (B), CA15-3 (C), CA19-9 (D), AFP (E), PSA (F) and fPSA (G) TMs were compared in the serum of 2072 individuals with each decade group compared to the other decades combined together in one group. Values are expressed as mean±SEM of 463 individuals (CEA), 158 individuals (CA125), 201 individuals (CA15-3), 247 individuals (CA19-9), 110 individuals (AFP), 535 individuals (PSA), 358 individuals (fPSA) and were compared using Mann–Whitney test with *, ** and ***representing p≤0.05, 0.01and 0.001 respectively.

and 3rd decades and high at the 7th and 8th decades with peak levels of 126.30±96.20 ng/mL. This result was in agreement with others (Li *et al*., 2021; Ashi *et al*., 2024). However, the age factor showed inconsistent trend when CEA levels in females compared with males at different age decades, where CEA levels were high in females in the 6*th* and 9*th* decades of age and high in males at 7*th* and 8*th* decades of age.

CA125 levels were higher than the normal range (≤35 U/mL) with mean±SEM of 111.2±48.25 U/mL. CA125 levels were higher in females than males with mean±SEM of 123.9±56.21 U/mL and 36.11±25.67 U/mL for female and male individuals respectively. This significant rise of CA125 levels in females was prominent at the 7th decade of age. Similar gender effect was cited earlier by other reports but at younger age (at the 3rd decade of age) and was attributed to the high sexual activity and inflammatory gynecological disorders at this age (Moore *et al*., 2012; Chen *et al*., 2024). Although this study reported non-significant rise in CA125 at the 5th and 6th decades, the significant rise of CA125 with age was documented in other studies and attributed to the hormonal changes during menopause (Yousefi *et al*., 2014; Anand & Choudhury, 2015; Wang *et al*., 2023; Chen *et al*., 2024). However, other studies reported decrease in CA125 at ≥50 years of age (Nah *et al*., 2023).

CA19-9 levels were higher than the normal range (≤39 U/mL) with mean±SEM of 53.17±10.94 U/mL. The levels of CA19-9 did not significantly vary between the tested gender groups. This finding was inconsistent with others who reported higher levels of CA19-9 in females (Feng *et al*., 2017; Zhang *et al*., 2018; Nah *et al*., 2023). However, the high levels of CA19-9 at the 9th decade of age observed in this study was in accordance with

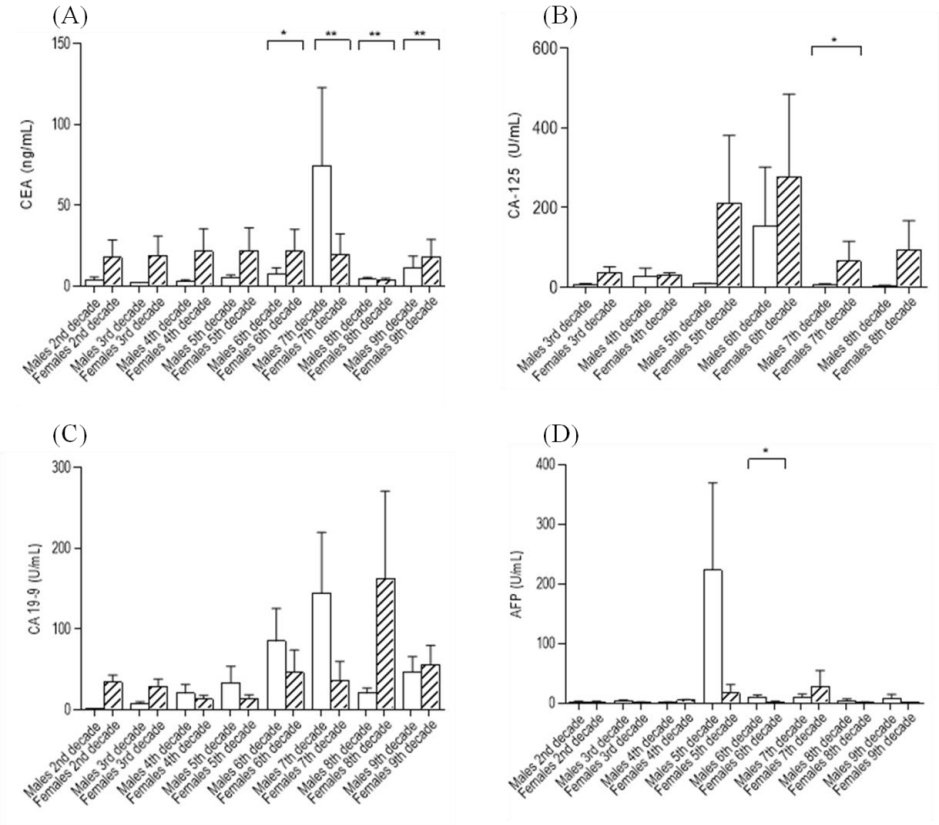


Figure 3. Tumor markers association with gender and age. The serum levels of CEA (A), CA125 (B), CA19-9 (C) and AFP (D) TMs were compared in the serum of 978 individuals and each male decade groups compared to the female decade groups. Values are expressed as mean±SEM of 463 individuals (CEA), 158 individuals (CA125), 247 individuals (CA19-9) and 110 individuals (AFP) and were compared using Mann–Whitney test with * and** representing p≤0.05 and 0.01 respectively.

previous works, which reported an increase of this marker with age (Zhang *et al*., 2018; Yang *et al*., 2019).

AFP levels were higher than the normal range (≤10 U/mL) with mean±SEM of 29.04±13.13 U/mL. With exception of the high level of this marker observed at the 1st decade of age, AFP levels were independent of age and gender. However, males showed higher AFP levels than females at the 6th decade of age. This was in line with Nah *et al.* (2023), who reported higher levels of AFP in males when compared to females.

PSA and fPSA levels were higher than the normal range (≤4.4 ng/mL and ≤1.0 ng/mL respectively) with mean±SEM of 5.60±0.61 ng/mL and 1.46±0.28 ng/mL respectively. PSA and free PSA levels showed similar results with low serum level at the 4th, 5th and 6th decade of age and high levels at the 8th and 9th decade of age. This PSA increase with age was in parallel with the high incidence of prostate cancer at age of 75 years or over, as previosly documented (Cepeda & Gammack, 2006).

CA15-3 levels were higher than the normal range (≤28 U/mL) with mean±SEM of 32.67±6.88 U/mL. CA15-3 levels were independent of age and gender. This finding was similar to that reported previously (Nah *et al*., 2023).

Conclusion

The current work has documented the serum values of many TMs in a Libyan population. The means of these values were higher than the normal reference range used in the present study. The differences in the serum values of TMs obtained from the participating individuals in this study were compared with similar literature findings and have proved possible association of gender and age risk factors with the circulating serum TMs.

Author contributions

Anwar M. Abdalmula designed the study, analyzed the data, interpreted the results and wrote the manuscript. Ashraf A. Zaied and Mahmoud A. Emsilakh collected the data. Fahima A. Alnagar worked to obtain the ethical approval and revised the manuscript draft.

Conflict of interest

The authors declare no conflict of interest in relation to the publication of this work.

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