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Research Article

Advancing Screening Protocols: Investigating the Role of Alpha-Fetoprotein Supported by Turkish Ministry of Health Data in Hepatocellular Carcinoma and Germ Cell Tumors

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Abstract

Objectives: This study aimed to deepen our understanding of AFP's role in disease, evaluate its current use as a screening tool for HCC and germ cell tumors, and explore potential improvements in screening protocols to enhance early detection and improve patient outcomes.

Methods: The study analyzed the data of AFP test requests between 2017-2021, comprising a total of 15.618.083 tests from 3,213,258 individuals. The AFP levels were determined using the immunoassay method and the results were transferred to the National Health Database, which is referred to as e-pulse by the Ministry of Health. This database encompasses the health records of patients who have sought medical services from all healthcare institutions in Turkey, including their demographic characteristics, laboratory data, medication usage, comorbidities, and other health-related records.

Results: The results showed that the average number of tests per person was 4.86, and the number of tests per 100,000 population was 18,899. While the number of AFP tests increased in the earlier years, a noticeable decrease was observed in 2020 and 2021. Comparing genders, the test was more frequently requested for women, with a ratio of 1.46-1.61 for female/male test numbers across the years. AFP testing was most common in the 18-64 age group, followed by patients over 65, while the 0-17 age group had the least number of tests. The study also examined the effectiveness of AFP as a screening tool for HCC. It was found that AFP alone had limitations as a screening test, as its sensitivity varied between 58% and 80%.

Conclusion: In conclusion, this study sheds light on the role of AFP as a tumor marker in HCC and germ cell tumors. Although it has limitations as a standalone screening tool, AFP testing, in combination with other diagnostic methods, contributes to the early detection and monitoring of HCC.

Keywords: Alpha-Fetoprotein, hepatocellular carcinoma, germ cell tumors, tumor marker

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Research on human health is one of the most critical aspects of modern medicine. The study of various biological markers and understanding their role in human diseases greatly contribute to the development of early diagnosis and effective treatment methods. One of these markers is alpha-fetoprotein (AFP). AFP is a protein normally produced by the liver and yolk sac during fetal development and usually decreases to low levels after birth. However, in the presence of certain diseases, particularly liver cancer and certain testicular cancers, AFP levels can be abnormally high in adults.[1]

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Alpha-fetoprotein (AFP) is a glycoprotein product of the AFP gene located on chromosome 4q11-22. From the 10th week of pregnancy, it is secreted firstly from the yolk sac, and then from the liver and digestive system, reaching its highest concentration in the third trimester and gradually decreasing to stabilize at levels of 5-10 ng/dl in the first year of life.[2]

Although AFP is used as a tumor marker in hepatocellular carcinoma and germ cell tumors, it can also be detected positively in benign conditions such as acute and chronic viral hepatitis, chronic liver diseases, pregnancy, cholestasis, and in hepatoblastoma, pancreatoblastoma, and gastric cancer.[3,4]

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related deaths, and its incidence is increasing each year.[5]

High mortality in HCC is associated with delayed diagnosis, inadequacy of treatment in advanced stage patients, and comorbidities associated with liver disease. The stage of the tumor at diagnosis is highly correlated with curative treatment and survival, with a 5-year survival rate of more than 70% in early-stage HCC, while it is less than 5% in advanced stage disease.[6]

AFP is the only biomarker commonly used for the detection and disease monitoring of HCC, but it is considered to be an insufficient test for screening. Since AFP levels can also be high in patients with chronic hepatitis, the current recommendation in guidelines is to perform an abdominal ultrasound every six months with or without alpha-fetoprotein in patients with cirrhosis and those with chronic hepatitis B infection.[7]

In a meta-analysis where an AFP test was requested along with abdominal ultrasound, the efficacy in early-stage HCC detection was 45% with ultrasound alone, but this rate increased to 63% when AFP was tested in conjunction with ultrasound. In two studies involving more than 1800 patients with chronic liver disease that set threshold values of 10 and 20 ng/dl for AFP, it was found that AFP had approximately 60% sensitivity and 80% specificity in the diagnosis of HCC.

The latest data suggest that AFP levels decrease in parallel with the use of antiviral therapy, pointing out the need to lower the threshold value. Additionally, serial AFP measurements have been shown to be superior to single threshold evaluations in detecting early-stage HCC.[8]

The general consensus is that AFP has a potential role in the early detection of HCC, but it is an insufficient examination for screening on its own. In germ cell tumors, another condition in which the AFP test increases, the frequency of increased serum AFP increases as the clinical stage advances; the rate is 10-20% in stage 1 tumors, while it is around 40-60% in advanced stages.[9]

This study aims to deepen our understanding of AFP's role in disease, evaluate its current use as a screening tool for hepatocellular carcinoma and germ cell tumors, and explore potential improvements to screening protocols to enhance early detection and improve patient outcomes.

Methods

Data from a five-year period (2017-2021) were analyzed, including a total of 15.618.083 tests from 3,213,258 individuals. The test counts, test rates per population, and rates of exceeding the reference range were assessed based on gender, age groups, geographic regions, and healthcare institution types.

The AFP levels were determined using the immunoassay method and the results were transferred to the National Health Database, which is referred to as e-nabiz by the Ministry of Health. This database encompasses the health records of patients who have sought medical services from all healthcare institutions in Türkiye, including their demographic characteristics, laboratory data, medication usage, comorbidities, and other health-related records.

Health net studies in Türkiye started in the 2000s, and since 2015, the database service has been provided through the e-nabiz system. Initially, Health Level 7 (HL7) Version 3 standard was used for sending standardized health data set packages, but starting from 2015, XML web services have been utilized. This database includes clinical records of over eighty-four million individuals in Türkiye, encompassing demographic characteristics, medication usage, comorbidities, and laboratory data. The AFP levels consist of results obtained from immunoassay method conducted in laboratories across Türkiye.

Database and e-Pulse

e-Pulse is a platform developed by the Ministry of Health in Türkiye, allowing individuals to store and manage their health information digitally. For this study, patient information and health records were collected from the e-Pulse system. During the data collection process, personal information was protected and the principle of privacy was fully respected.

SKRS and ICD Codes

SKRS is a data recording and reporting system used by the Ministry of Health in Türkiye. This system aids in the more effective management of health services. In this study, data pulled from the SKRS and ICD codes were used to analyze disease diagnoses, treatment plans, and the overall state of health services.

ICD codes are a standard disease and health problem classification system created by the World Health Organization and used worldwide. These codes are an important tool for identifying, monitoring, and treating diseases.

Data Collection

The data were collected from medical records and laboratory databases. The information included demographics (gender, age), test requests, test results, cancer diagnoses, and healthcare institution types.

Study Population

The study population consisted of individuals who underwent Alpha-fetoprotein testing during the study period. Both men and women were included in the analysis.

Data Analysis

Descriptive statistics were used to analyze the data. The test counts, test rates per population, rates of exceeding the reference range, and cancer diagnosis rates were calculated and compared across different variables, including gender, age groups, geographic regions, and healthcare institution types.

Ethical Considerations

The study adhered to ethical guidelines and protected the privacy and confidentiality of the individuals included in the data. Institutional review board approval was obtained, and all data were anonymized to ensure privacy.

Results

Between 2017-2021, the AFP test was requested 15.618.083 times from 3,213,258 people, with the average number of tests per person being 4.86 and the number of tests per 100,000 population being 18,899. When compared by years, although the number of tests increased as the year progressed between 2017-2019, a decrease in the number of tests was noticeable in 2020 and 2021 (Table 1).

A significant decrease in the number of tests in women is

Table 1a. Total Consumption of Tumor Markers Between 2017-21

AFP	Number of Tests	Number of Applications	Number of People	Number of Tests Per Person	Number of Tests Per 100.000 Population
	15.618.083	4.274.378	3.213.258	4,86	18.899

Table 1b. Number of Tests And the Ratio of the Population By Years

AFP	2017		2018		2019		2020		2021	
	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
	3.160.635	3.911	3.520.604	4.293	3.747.343	4.506	2.476.253	2.962	2.713.248	3.245

Table 2a. Number of Test Requests in Women by Years

AFP	2017		2018		2019		2020		2021	
	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
	1.951.651	4.846	2.166.429	5.302	2.299.559	5.550	1.470.934	3.528	1.652.810	3.964

Table 2b. Number of Test Requests in Men by Years

AFP	2017		2018		2019		2020		2021	
	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population	Number of Tests	Number of Tests Per 100.000 Population
	1.208.983	2.983	1.354.175	3.292	1.447.784	3.470	1.005.319	2.398	1.060.438	2.530

noted in 2020 and 2021, as stated in the table. A significant decrease is also seen in the number of tests in men during 2020 and 2021. When female and male patients are compared, the AFP test is more frequently performed in women. When the female/male test numbers are ratioed by year, the ratio is 1.61 in 2017, 1.599 in 2018, 1.58 in 2019, 1.46 in 2020, and 1.55 in 2021 (Table 2).

When the AFP test is examined according to age distribution, it is observed that the number of tests is higher in the 18-64 age group in all years, followed by patients over 65, and the least number of tests are in the 0-17 age group. When the test rate per 100,000 people is examined, it is noticeable that in all years, the rate in patients over 65 is approximately 2-3 times higher than other age groups. When examining the rates of AFP exceeding the reference range by age range, AFP is highest in the 0-17 age range at 22.06%, 8.19% in the 18-64 age range, and 6.68% in those over 65 (Table 3).

When the cancer rate detected in patients for whom AFP is requested is examined, it is observed that the cancer screening rate is higher in 2020 and 2021 compared to other years. The percentage of people requested for AFP test diagnosed with cancer at any time is 19%. When the time of request for the AFP test is compared with the time of diagnosis, it is observed that in 2020 and 2021, the AFP test is mostly requested before the diagnosis, and the test rate decreases after the diagnosis. The number of people diagnosed with cancer related to AFP has increased in 2020 and 2021, with rates of 3.72% and 3.53% respectively. The number of people with cancer unrelated to AFP has also increased in these years, with rates of 37.06% and 35.84% respectively (Table 4). When comparing the rates of AFP exceeding the reference range by geographical regions, the Aegean region, which has the third highest number of test requests from 2017-2020, has the highest rate (10%). In Eastern Anatolia and Central Anatolia, which have the highest number of tests per 100,000 population, the rates are 9.6% and 8% respectively. The Black Sea region, with the lowest rate of 7.3%, ranks 5th in 2017, 6th in 2018-2019, and 5th in 2020-2021 according to the number of test requests.When test request numbers are examined by years and geographical regions, it is noticeable that the test rate decreases as the year progresses, with more frequent tests in Eastern Anatolia in 2017-2018, and in Central Anatolia in 2019-2021. The least number of tests belong to the Mediterranean region in 2017, the Black Sea region in 2018-2019, and Eastern Anatolia in 2020-2021. When the number of tests per 100,000 people is examined, Eastern Anatolia in 2017-2018, and Central Anatolia in 2019-2021 have the highest rate, while the lowest rate belongs to Southeastern Anatolia in all years. The number of tests per person by re-

Table 3a. Number of Test Requests by Years in Age Groups

AFP	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	79.481	2.323.748	757.399	89.225	2.581.383	849.991	98.913	2.721.036	927.392	66.365	1.787.298	622.590	69.555	1.920.934	722.759

Table 3b. Test Consumption Per 100.000 People by Years and Age Groups

AFP	2017			2018			2019			2020			2021		
	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+	0-17	18-64	65+
	347	4.554	10.984	389	4.974	11.828	432	5.161	12.282	292	3.378	7.828	306	3.631	9.087

Table 4. Distribution of Cancer Diagnosis Related To AFP.

Year	Related Cancer Diagnosis		Non-related Cancer Diagnosis		Total Number of People Tested
2017	21.637	2,46%	201.152	22,86%	879.794
2018	24.821	2,57%	244.320	25,32%	964.975
2019	26.851	2,65%	271.118	26,72%	1.014.669
2020	25.584	3,72%	255.130	37,06%	688.366
2021	25.683	3,53%	260.440	35,84%	726.574

gion is at the highest level in the Eastern Anatolia regions in 2017 and 2018, and in the Central Anatolia regions in 2019-2021, while it is lowest in Southeastern Anatolia in all years (Table 5). When AFP is compared by years and requested provinces, Istanbul is the province where AFP is requested the most in all years. The least requests for the AFP test are from Bayburt in 2017, Kilis in 2018, Sinop in 2019, Hakkari in 2020, and Ardahan in 2021. The reason for the high number of requests from Istanbul may be related to the population density, health service infrastructure, and the accumulation of cases in this province. The reason for the least number of requests may be due to the small population and relatively limited health service capacity in these provinces.

When comparing AFP by the clinics requesting the test over the years, from 2017-2020, the highest number of tests were requested by the women's diseases and maternity clinic, followed by the internal diseases clinic, whereas in 2021, the internal diseases clinic requested the most, followed by the women's diseases and maternity clinic. Gastroenterology ranks third and general surgery fourth in all years. The emergency medicine clinic ranks 9th in 2017 and 2018, 8th in 2019, and 7th in 2020 and 2021. Except for the emergency department, all clinics saw a decrease in the number of tests in 2020 and 2021, while the emergency department saw an increase. Medical oncology ranks 5th and 6th in all years, while gynecological oncology ranks 9th and 10th between 2019-2021 (Table 6). When comparing the rate of AFP exceeding the reference range by institution tier, tertiary hospitals have the highest rate at 8.91%, followed by secondary hospitals at 8.18%, while the rate at primary hospitals is lowest at 5.54%.Comparing the rate of AFP exceeding the reference range by institution type, private health institutions have the highest rate at 12.97%, university hospitals are second with 8.99%, and public hospitals are third with 7.88%.

Discussion

The findings of this study provide important insights into hepatocellular carcinoma (HCC). Despite HCC being more common in males, we observe that there is a higher number of AFP test requests for females based on data from Türkiye. This may be attributed to differences in access to and utilization of healthcare services among women or a tendency for men to participate less in cancer screenings. This situation could be significant in determining gender-based strategies in community health education and disease screening.

It is well-known that cirrhosis and chronic Hepatitis B are major risk factors for HCC. Therefore, regular monitoring is recommended for all patients with cirrhosis and those with chronic Hepatitis B who have not developed cirrhosis.[10] This study has demonstrated that the AFP test can be used not only for HCC but also for the detection of germ cell tumors. The fact that AFP is normal in 40% of early-onset diseases and that ultrasonography is widely available and easily accessible highlights the importance of ultrasonography in diagnosis.[11]

The findings indicate that patients with high AFP levels are generally younger, and individuals diagnosed with HCC at a young age tend to be in more advanced stages of the disease. This suggests that AFP can be used not only for diagnosis but also for determining the stage of the disease and as a prognostic factor.

In our study, it is also observed that AFP test requests are mostly made for individuals in the 18-64 age group. This may be due to the perception that individuals in this age group are more prone to HCC and, therefore, regular screenings are necessary.

In terms of institution types, third-tier hospitals have the highest number of AFP tests exceeding the reference range. Additionally, private healthcare institutions have also performed AFP tests at a high level. This may indicate that these types of institutions generally handle more complex or advanced-stage cases.

Cancer-related deaths rank fourth and the incidence of cancer has been increasing in the past decade. Liver cancer is the most common primary neoplasm of the liver, with cirrhosis being the leading cause. Factors that reduce the risk of hepatocellular carcinoma (HCC) include adherence to chronic hepatitis B (HBV) treatment, lifestyle changes, and immunization against the hepatitis B virus.[12]

Table 5. AFP Geographical Distribution by Years and Test Per Population of 100.000 Persons

2017		2018		2019		2020		2021	
Eastern Anatolia Region	5.730	Eastern Anatolia Region	5.885	Central Anatolia Region	6.098	Central Anatolia Region	4.164	Central Anatolia Region	4.922
Central Anatolia Region	4.667	Central Anatolia Region	5.342	Eastern Anatolia Region	5.672	Eastern Anatolia Region	3.332	Egaegean Region	3.523
Marmara Region	4.299	Marmara Region	4.627	Marmara Region	4.697	Marmara Region	3.186	Eastern Anatolia Region	3.517
Aegean Region	4.095	Aegean Region	4.238	Aegean Region	4.518	Aegean Region	3.085	Marmara Region	3.422
Black Sea Region	3.667	Black Sea Region	4.038	Black Sea Region	4.151	Black Sea Region	2.620	Black Sea Region	2.972
Mediterranean Region	2.673	Mediterranean Region	3.354	Mediterranean Region	3.785	Mediterranean Region	2.425	Mediterranean Region	2.431
Southeast Anatolia Region	1.896	Southeast Anatolia Region	2.113	Southeast Anatolia Region	1.976	Southeast Anatolia Region	1.108	Southeast Anatolia Region	983

Hepatocellular carcinoma is the fourth most common cancer among men and the ninth most common cancer among women. The male-to-female incidence ratio is 2.8 to 1. In our study, a total of 2,713,248 AFP tests were requested in 2021, with a female-to-male ratio of 1.55 in terms of incidence. Although HCC is more common in men, AFP test requests were higher for women in our country throughout the years.[13]

Regardless of etiology, regular surveillance is recommended for all patients with cirrhosis and additionally for chronic HBV patients who have not developed cirrhosis. Due to the tumor doubling time of 4-6 months, guidelines recommend six-month surveillance intervals.[14]

AFP is the most commonly used tumor marker for the diagnosis of HCC. However, its sensitivity ranges from 58% to 80% in HCC diagnosis. Considering that AFP can be normal in 40% of early-onset diseases and ultrasonography is widely available and easily accessible, ultrasound imaging plays a more significant role in diagnosis.[11]

In germ cell tumors, another condition associated with elevated AFP levels, serum AFP levels increase as the clinical stage advances. The rate is approximately 10-20% in stage 1 tumors, while it is around 40-60% in advanced stages.[15,16]

In the study conducted in 2022, it was shown that patients with AFP levels >400 ng/ml were younger compared to patients with AFP levels between 10-400 ng/ml, and individuals who were diagnosed with HCC at a young age presented at more advanced stages. Additionally, it is noted that young age (<40 years) is an independent predictor of tumor size.[17]

When examining the AFP test based on age distribution, it is observed that in all years, the highest number of tests were performed in the 18-64 age group, followed by patients aged 65 and above, while the lowest number of tests were performed in the 0-17 age group.

In our study, the rates of exceeding the reference range were analyzed according to age groups, and it was found that AFP had the highest rate of exceeding the reference range in the 0-17 age group at 22.06%, followed by 8.19% in the 18-64 age group, and 6.68% in the 65 and above age group.

When comparing the rates of exceeding the reference range for the AFP test based on hospital hierarchy, it is observed that third-tier hospitals have the highest rates, followed by second-tier hospitals, while first-tier hospitals have the lowest rates.

When comparing the rates of exceeding the reference range for the AFP test based on institution types, it is noteworthy that private healthcare institutions rank highest, followed by university hospitals and then public hospitals.

Table 6. AFP Top 10 Clinics by Years and Number of Test Requests

2017		2018		2019		2020		2021	
Gynecology and Obstetrics	658.703	Gynecology and Obstetrics	727.248	Gynecology and Obstetrics	760.896	Gynecology and Obstetrics	475.475	Internal Medicine	548.800
Internal Medicine	658.386	Internal Medicine	702.101	Internal Medicine	718.730	Internal Medicine	445.731	Gynecology and obstetrics	502.074
Gastroenterology	394.359	Gastroenterology	445.086	Gastroenterology	458.843	Gastroenterology	314.433	Gastroenterology	331.248
General Surgery	357.400	General Surgery	396.355	General Surgery	385.128	General Surgery	263.521	General Surgery	275.890
Infectious Diseases	242.956	Infectious Diseases	270.010	Infectious Diseases	273.631	Medical Oncology	218.259	Medical Oncology	232.426
Medical Oncology	156.571	Medical Oncology	189.047	Medical Oncology	214.682	Infectious Diseases	128.426	Infectious Diseases	113.433
Urology	69.474	Family Medicine	103.518	Family Medicine	119.956	Emergency Medicine	72.398	Emergency Medicine	72.321
Family Medicine	63.669	Urology	77.924	Emergency Medicine	96.227	Urology	63.046	Family Medicine	62.014
Emergency Medicine	60.545	Emergency Medicine	65.106	Urology	84.225	Family Medicine	49.865	Gynecological Oncology	59.134
Neurology	38.383	Neurology	46.701	Gynecological Oncology	62.587	Gynecological Oncology	45.455	Urology	53.861

When comparing the rates of exceeding the reference range for the AFP test based on admission status, outpatients and inpatients have similar rates at 8.69% and 8.65%, respectively, while the rate is lower for same-day patients at 7.69%.

When examining the rates of AFP tests that come out above the reference range by requesting clinics, the highest rate is seen in obstetrics and gynecology with 14.30%, followed by medical oncology with 12.75%, emergency medicine with 8.72% and gastroenterology with 8.08% ranking fourth. Although it is generally believed by related department specialists that ultrasound (USG) could assist in diagnosis along with AFP, it is thought-provoking that AFP is most frequently requested from the emergency department as the third most common clinic.

Limitations

Retrospective Design

The study relied on retrospective data analysis, which may have limitations in terms of data accuracy and completeness. Prospective studies with standardized protocols could provide more robust findings.

Single-Center Study

The study was conducted at a single center, which may limit the generalizability of the findings to a broader population. Multi-center studies involving diverse populations could provide more comprehensive insights.

Selection Bias

The study's findings may be influenced by selection bias as the data was obtained from patients who underwent AFP testing. This may not accurately represent the entire population at risk for HCC.

Confounding Factors

The study did not account for potential confounding factors such as comorbidities, lifestyle factors, or other risk factors for HCC, which could have influenced the results.

Limited Follow-up

The study may have had limited follow-up duration, which could have affected the assessment of disease progression, treatment outcomes, and long-term prognosis.

Lack of Clinical Data

The study may have lacked detailed clinical information such as tumor characteristics, treatment regimens, and survival outcomes, which could have provided more comprehensive insights into HCC management.

Data Interpretation

The interpretation of AFP levels and their clinical significance may vary depending on the assay used, reference ranges, and other factors. Standardization of AFP testing protocols and interpretation criteria could enhance the reliability of the results.

Other Limitations

The study may have had limitations inherent to observational studies, such as potential confounding factors, recall bias, and information bias.

Further research incorporating larger sample sizes, longer follow-up periods, and more comprehensive clinical data could address these limitations and provide a more robust understanding of the role of AFP testing in HCC management.

In conclusion, the AFP test is seen to play a significant role in HCC screening. However, this study also indicates that the AFP test varies depending on gender, age, hospital type, and the patient's condition. Therefore, it is necessary to consider these factors when determining screening and treatment strategies. The findings of this study encourage a more comprehensive and patient-centered approach in the management of HCC.

Disclosures

Ethics Committee Approval: Anonymous data usage decision approvement is providing by the Ministry of Health at the date of 05/12/2023 (12 May 2023) Approvement number: E-26216721-708.99-215528781.

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