



The Diagnostic Rate and Clinical Implications of Neuron-Specific Enolase in Neuroendocrine Tumors and Small Cell Lung Cancer: Data from the Ministry of Health of the Republic of Turkey

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Abstract

Aim: Neuron-specific enolase (NSE) is a widely used tumor marker for the diagnosis of neuroendocrine tumors and small cell lung cancer (SCLC). This study aimed to evaluate the utilization, diagnostic rate, distribution by gender and age groups, and variation in test requests across different healthcare institutions for NSE.

Methods: A cross-sectional analysis based on Data from the Ministry of Health of the Republic of Turkey data from 2017 to 2021 was conducted. Neuron-specific enolase tests were requested from a total of 24,763 individuals, and the results of 110,401 tests were evaluated.

Results: Neuron-specific enolase has emerged as the most commonly requested tumor marker in pediatric hematology and oncology clinics. Compared to other tumor markers (cancer antigen 19-9, carcinoembryonic antigen, cancer antigen 15-3 etc.), NSE testing demonstrated the highest diagnostic rate. The test was predominantly requested prior to or simultaneously with the diagnosis and less frequently after the diagnosis. NSE testing showed a higher positivity rate in individuals with confirmed neuroendocrine tumors and SCLC than in others. Moreover, public, training, research, and university hospitals requested NSE tests more than other institutions.

Conclusion: Neuron-specific enolase plays a significant role as a valuable tumor marker in the diagnosis of neuroendocrine tumors and SCLC. This study highlights the diagnostic rate, utilization in pediatric hematology and oncology clinics, and variations across healthcare institutions.. The findings of this study can guide clinicians and researchers in the management of these malignancies.

Keywords: Neuron-specific enolase, biomarkers, tumor

Introduction

Neuron-specific enolase (NSE) is an isoform of the enzyme enolase that is specifically expressed in neurons within the nervous system. This isoform is closely associated with the development, function, and diseases of the nervous system. The primary function of NSE is to participate in the conversion of glucose to energy through the glycolysis pathway. Neuron-specific enolase is particularly regarded as a key enzyme in neuronal energy production, and due to this characteristic, it serves as an important biomarker in the investigation of nervous system disorders. Neuron-specific enolase is highly

expressed, particularly in neuroendocrine tumors. These tumors are non-neuronal in origin but possess neuronal features. The NSE is employed as an indicator to assess the neuronal differentiation and the degree of malignancy in such tumors. Elevated NSE levels serve as a significant clinical tool in the diagnosis, prognosis evaluation, and monitoring of treatment response in neuroendocrine tumors. In cases of neuronal damage, NSE levels increase in the blood because of neuronal degradation. In addition, elevated NSE levels are observed in conditions such as brain injury, traumatic brain injury, ischemic stroke, and neurodegenerative diseases. Therefore, NSE is a valuable



biomarker for the early detection of neurological damage and monitoring the treatment response (1).

Neuron-specific enolase is a tumor marker used in the diagnosis of neuroendocrine tumors and small cell lung cancer (SCLC). Small cell lung cancer, which accounts for 10-20% of lung cancers, is the most malignant type and is also the most responsive to chemotherapy and radiation therapy (2). However, it carries a high risk of recurrence and distant metastasis, with a 5-year survival rate of less than 5% (3). Neuron-specific enolase serum concentration has been found to be positively associated with tumor size, advanced tumor stage, and distant metastasis. Additionally, it is believed to have a promising role in predicting the response to chemotherapy and radiation therapy (4).

The aim of this article is to analyze on the clinical significance of NSE as a tumor marker in the diagnosis and prognosis evaluation of neuroendocrine tumors and SCLC, as well as to increase awareness on the subject, identify clinician trends, and guide the correct use of tumor markers in this way.

Methods

Compliance with Ethical Standards

Ethical approval for the study was obtained from the Ministry of Health of Turkey General Directorate of Health Information Systems (approval no: 95741342-020, date: 27.11.2019), and all data were anonymized to ensure privacy. This study adhered to ethical guidelines and protected the privacy and confidentiality of the individuals included in the data.

Study Design

This cross-sectional study utilized data from the Ministry of Health, covering a five-year period from 2017 to 2021, including 110,401 tests from 24,763 individuals. The data included information on NSE tests requested from individuals across different regions and healthcare institutions in the country. The test counts were evaluated in detail. Neuron-specific enolase levels represent the results obtained through the immunoassay method and were derived using the E-Nabiz system of the Turkish Ministry of Health. The ministry's database is referred to as e-Nabiz. This database encompasses the health records of patients who have sought medical services from all healthcare institutions in Turkey, including demographic characteristics, laboratory data, medication usage, comorbidities, and other health-related records.

Study Population

The study population comprised individuals who underwent NSE testing during the study period. Both men and women were included in the analysis.

Data Collection

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

Database and e-Pulse

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

Health Coding Reference Server and International Classification of Diseases Codes

Health Coding Reference Server (SKRS) is a data recording and reporting system used by the Ministry of Health in Turkey. This system aids in the more effective management of health services. In this study, data pulled from the SKRS and International Classification of Diseases codes were used to analyze disease diagnoses, treatment plans, and the overall state of health services. International Classification of Diseases codes are a standard disease and health problem classification system created by the World Health Organization and used worldwide. These codes are important tools for identifying, monitoring, and treating diseases.

Statistical 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.

When comparing the number of NSE tests by year, it was observed that the test count and tests per 100,000 population increased between 2017 and 2019, but showed a significant decrease in 2020 and 2021 (Figure 1).

In terms of test requests by gender, similar to the general population, the number of test requests for females increased as the years progressed between 2017 and 2019, but exhibited a significant decrease in 2020 and 2021. Neuron-specific enolase ranked sixth among the tumor markers tested in females across all years.

Similarly, for males, the number of test requests increased as the years progressed between 2017 and 2019, but showed a notable decrease in 2020 and 2021.

When the number of test requests for females and males was compared by year, the ratio was 1/1.16 in 2017,

1/1.07 in 2018, 1/1.09 in 2019, 1.19 in 2020, and 1/14 in 2021. Except for NSE and PSA, all other tumor markers were more frequently requested for female patients in all years (Table 1).

In terms of test consumption per 100,000 population, NSE had the lowest rate in the 18-64 age range, followed by the 0-17 age range, and the highest rate was observed in the 65 and older age group. Among the other tumor markers, the lowest rate was observed in the 0-17 age group, the second lowest in the 18-64 age group, and the highest rate was observed in the 65 and older age group

	NUMBER OF TESTS	NUMBER OF APPLICATIONS	NUMBER OF PEOPLE	NUMBER OF TESTS PER PERSON	NUMBER OF TESTS PER 100,000 POPULATION
AFP	15.618.083	4.274.378	3.213.258	4,86	18.899
CA125	22.680.568	5.120.380	3.917.240	5,79	27.445
CA153	21.579.044	4.077.373	2.981.142	7,24	26.112
CA199	25.808.137	5.251.969	4.018.913	6,42	31.230
CA724	911.834	160.519	141.974	6,42	1.103
CEA	27.394.778	5.533.959	4.016.178	6,82	33.150
NSE	110.401	29.969	24.763	4,46	134
PSA FREE	12.876.151	4.336.930	3.020.756	4,26	15.581
PSA TOTAL	21.547.232	9.608.915	5.812.043	3,71	26.074

Figure 1. Total consumption of tumor markers between 2017-2021

(Table 2).

When comparing the rates of receiving a cancer diagnosis at any time for individuals who underwent NSE testing, in 2017, 63% of individuals received a cancer diagnosis, whereas in 2018, 71% did, 56% in 2019, 57% in 2020, and 52% in 2021. Among individuals who had tumor markers requested, NSE had the highest diagnostic percentage in all years (Table 3).

When analyzing the test request timing in relation to the diagnosis of patients, except for 2017, in other years, the tests were requested more frequently before the diagnosis, followed by simultaneous requests with the diagnosis, and the least requests were made after the diagnosis (in 2017, most requests were made at the time of diagnosis) (Table 4).

Neuron-specific enolase tests were most frequently requested in the Marmara region. The second most frequent region was the Mediterranean region in 2017, the Eastern Anatolia region between 2018 and 2019, and the Central Anatolia region between 2020 and 2021. The region with the lowest test requests was consistently the Black Sea region. When comparing the Marmara region, which ranked first in 2021, with the last-ranked Black Sea region, the ratio was 85.

When analyzing the test requests per 100,000 population by geographic region, in 2017, the highest rate was observed in the Mediterranean region, while between 2018 and 2019, it was the Eastern Anatolia region, and between 2020 and 2021, it was the Marmara region. The lowest region was consistently the Black Sea region. When comparing the Marmara region with the second-ranked Central Anatolia region in 2021, the ratio was

	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+
NSE	5.767	7.095	3.272	7.003	11.555	5.819	9.445	10.933	5.734	8.085	8.702	4.687	7.145	9.529	5.630

NSE: Neuron-specific enolase

	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+
NSE	25	14	47	31	22	81	41	21	76	36	16	59	31	18	71

NSE: Neuron-specific enolase

	2017		2018		2019		2020		2021	
	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer	No diagnosis of cancer	Diagnosis of cancer
NSE	37%	63%	29%	71%	44%	56%	43%	57%	48%	52%

NSE: Neuron-specific enolase

1.07, and when compared with the lowest-ranking Black Sea region, the ratio was 21 (Table 5).

When comparing the test requests by clinics, medical oncology had the highest number of test requests in all years. Pediatric hematology and oncology ranked second. Dermatology and venereal diseases, pediatrics, and internal medicine clinics ranked third. The internal medicine clinic ranked seventh in 2017 and fifth in 2019. Family medicine did not appear in the top 10 clinics. The emergency medicine clinic ranked 10th in 2017 and 2020 and ninth in 2018 (Figure 2).

When the diagnoses entered in the test request applications were examined, in 2017, the most common diagnoses were malignant neoplasms of the skin, while in 2018 and 2020, it was an unspecified malignant neoplasm, and in 2019 and 2021, it was vitamin D deficiency and unspecified diagnoses. Overall, the most common diagnoses over the five years were malignant neoplasms in an unspecified region, followed by vitamin D deficiency and unspecified diagnoses, and pain not classified elsewhere.

When comparing the rates of exceeding the reference range of the test, the highest rate was observed in 2017 at 74.30%, while the lowest rate was 52.15% in 2021,

showing a decrease as the years progressed. Neuron-specific enolase had the highest rate of exceeding the reference range among all tumor markers.

When the rates of exceeding the reference range were compared based on the healthcare level, the highest rate of 64.32% was observed in the tertiary level, followed by 55.11% in the secondary level and 51.01% in the primary level institutions.

Based on the institution type, when the rates of exceeding the reference range were examined, the overall rate was 63.00%, with the highest rate being 73.78% in public and training and research hospitals, followed by 58.13% in university hospitals, and 53.44% in private healthcare institutions. Neuron-specific enolase had the highest rate in public, training and research hospitals, whereas other tumor markers had the lowest rate in public, training, and research hospitals.

When analyzing the rates of exceeding the reference range by geographic regions, the highest rate of 91.8% was observed in the Eastern Anatolia region in 2018 and 2019, which had the highest test requests and tests per 100,000 population. The second-highest rate of 82.2% was observed in the Southeast Anatolia region, which had the lowest number of tests per 100,000 people. The lowest

Table 4. Distribution of cancer diagnoses related to NSE

Year	Related cancer diagnosis		Non-related cancer diagnosis		Total number of people tested
2017	1,812	40.61%	3,960	88.75%	4,462
2018	2,363	38.97%	5,345	88.16%	6,063
2019	2,763	38.20%	5,953	82.30%	7,233
2020	2,744	45.71%	5,918	98.58%	6,003
2021	2,757	44.41%	5,929	95.51%	6,208

NSE: Neuron-specific enolase

Table 5. Geographical distribution by NSE years and number of test requests

2017		2018		2019		2020		2021	
Region	Number of tests	Region	Number of tests	Region	Number of tests	Region	Number of tests	Region	Number of tests
Marmara Region	7,450	Marmara Region	8,121	Marmara Region	9,761	Marmara Region	9,468	Marmara Region	10,883
Mediterranean Region	3,120	Eastern Anatolia Region	7,464	Eastern Anatolia Region	6,048	Central Anatolia Region	4,629	Central Anatolia Region	5,203
Central Anatolia Region	2,427	Central Anatolia Region	3,687	Central Anatolia Region	4,244	Mediterranean Region	3,360	Aegean Region	2,797
Eastern Anatolia Region	1,628	Mediterranean Region	3,185	Mediterranean Region	3,592	Egeaean Region	2,589	Mediterranean Region	1,996
Aegean Region	1,339	Aegean Region	1,641	Aegean Region	1,957	Eastern Anatolia Region	1,081	Eastern Anatolia Region	1,004
Southeast Anatolia Region	115	Southeast Anatolia Region	187	Southeast Anatolia Region	398	Southeast Anatolia Region	270	Southeast Anatolia Region	293
Black Sea Region	55	Black Sea Region	92	Black Sea Region	112	Black Sea Region	77	Black Sea Region	128

NSE: Neuron-specific enolase

2017		2018		2019		2020		2021	
MEDICAL ONCOLOGY	3.368	MEDICAL ONCOLOGY	10.200	MEDICAL ONCOLOGY	8.347	MEDICAL ONCOLOGY	5.575	MEDICAL ONCOLOGY	4.630
CHILDRENS HEMATOLOGY AND ONCOLOGY	3.056	CHILDRENS HEMATOLOGY AND ONCOLOGY	3.886	CHILDRENS HEMATOLOGY AND ONCOLOGY	5.080	CHILDRENS HEMATOLOGY AND ONCOLOGY	4.465	CHILDRENS HEMATOLOGY AND ONCOLOGY	3.901
DERMATOLOGY	1.804	DERMATOLOGY	2.014	CHILD HEALTH AND DISEASES	1.894	CHILD HEALTH AND DISEASES	1.573	DERMATOLOGY	2.535
CHILD HEALTH AND DISEASES	1.125	CHILD HEALTH AND DISEASES	1.363	NEUROLOGY	1.790	NEUROLOGY	1.504	NEUROLOGY	1.538
RADIATION ONCOLOGY	880	NEUROLOGY	1.097	INTERNAL MEDICINE	1.038	DERMATOLOGY	1.159	CHILD HEALTH AND DISEASES	1.449
NEUROLOGY	869	INTERNAL MEDICINE	795	CHEST MEDICINE	901	CHILD SURGERY	754	INTERNAL MEDICINE	1.042
INTERNAL MEDICINE	685	CHILD SURGERY	477	CHILD NEUROLOGY	723	INTERNAL MEDICINE	741	GENERAL SURGERY	698
MEDICAL BIOCHEMISTRY	472	MEDICAL BIOCHEMISTRY	460	DERMATOLOGY	599	CHEST MEDICINE	692	CHEST MEDICINE	652
GASTROENTEROLOGY	432	EMERGENCY MEDICINE	428	ENDOCRINOLOGY AND METABOLISM DISEASES	584	GENERAL SURGERY	612	CHILD SURGERY	643
EMERGENCY MEDICINE	419	CHEST MEDICINE	323	CHILD SURGERY	555	EMERGENCY MEDICINE	592	GASTROENTEROLOGY	642

Figure 2. NSE top 10 clinics according to the years and the number of tests requests

rate of 51.3% was observed in the Black Sea region.

In terms of gender, when examining the rates of exceeding the reference range, it was generally 62.48%, with 65.11% in males and 59.40% in females. The NSE had the highest rate of exceeding the reference range among all tests.

When analyzing the rates of exceeding the reference range by age groups, the highest rate of 74.90% was observed in the 0-17 age group, followed by 49.19% in the 65 and older age group, and 10.44% in the 18-64 age group. When comparing the age groups (0-17/18-64/65 and older) in terms of rates, the ratios were calculated as 1.62/1/1.06.

When analyzing the rates of exceeding the reference range by admission status, it was observed that the highest rate of 66.11% was for inpatients, followed by 62.46% for outpatients, and 57.85% for day patients. When compared in order (inpatient/outpatient/day patient), the ratios were calculated as 1.14/1.07/1. Neuron-specific enolase had the highest rate of exceeding the reference range among all tumor markers for all groups.

When analyzing the rates of exceeding the reference range in the presence of a cancer diagnosis, a total of 62.93% of individuals tested positive. Among them, 63.36% had a cancer diagnosis, whereas 62.22% did not. The NSE had the highest rate of exceeding the reference range among all tests, regardless of the presence of a cancer diagnosis.

In terms of the clinics that requested NSE tests, when examining the rates of tests exceeding the reference range, the highest rate of 75.43% was observed in the Pediatric Hematology and Oncology clinic, followed by 74.61% in the Pediatric Surgery clinic, and 72.83% in the Pediatric Neurology clinic. Among all clinics, tumor marker tests were most frequently requested by the medical oncology

clinic, with a rate of 55.90%. The Pediatric Hematology and Oncology clinic ranked second, with a rate of 75.43% (top-ranked). The Dermatology and Venereal Diseases Clinic, which ranked third in all years, had a rate of 17.76%, which was the lowest among the top 10 clinics. Family medicine and emergency medicine clinics did not appear among the top 10 clinics.

Discussion

The findings of our study revealed several important aspects regarding the clinical utility of NSE as a tumor marker. Pediatric hematology and oncology clinics have emerged as the primary settings where NSE testing is most commonly requested, indicating its significance in the evaluation of pediatric malignancies. Moreover, our results demonstrated that NSE exhibited the highest diagnostic rate compared to other tumor markers, underscoring its effectiveness in the diagnosis of neuroendocrine tumors and SCLC. Interestingly, NSE test requests predominantly occurred before or simultaneously with the diagnosis, suggesting its role as an initial screening tool in the diagnostic workup. In contrast, NSE testing was less frequently performed after the confirmation of the diagnosis. Notably, our study showed a higher positivity rate for NSE among individuals with a confirmed cancer diagnosis, further supporting its clinical relevance in detecting cancer-related abnormalities. Additionally, the higher frequency of NSE test requests observed in public, training and research hospitals and university hospitals suggests widespread recognition and utilization of NSE in these healthcare settings. Remarkably, NSE test results frequently exceeded the reference range, setting it apart from other tumor markers and highlighting its potential as a reliable indicator for the presence of underlying malignancies.

SCLC, which accounts for 10-20% of lung cancers, is the most malignant type and the most responsive to chemotherapy and radiotherapy. Although SCLC is generally more common in males, there has been an increase in the number of cases in females worldwide over the past 50 years (5).

A study by Lee et al. (6) included 262,826 patients diagnosed with SCLC. The patients were grouped based on age distribution, with 8,792 (5.1%) between 18 and 50 years, 96,721 (56.1%) between 50 and 70 years, and 66,940 (38.8%) aged 70 years. The median age of the study population was 66 (6). In our study, when comparing the number of test requests by age groups, NSE was most frequently requested in the 18-64 age group, followed by the 0-17 age group, and the least frequently requested in the age group of 65 and above.

A study by Lu et al. (7) demonstrated that NSE supports the stem-cell-like properties of SCLC through the neuroblastoma suppressor of tumorigenicity 1 (NBL1) pathway and activates the BMP2/Smad/ID1 pathway (1). In our study, it was not possible to distinguish between the "NSE supports the stem-cell-like properties of SCLC through the NBL1 pathway and activates the BMP2/Smad/ID1 pathway" based on retrospective data analysis. The evolution of diagnostic technologies has potentially enhanced the accuracy and reach of NSE testing, making it a more sought-after method.

As medical professionals become more aware of the intricacies of pediatric malignancies, there seems to be a gravitation towards early and effective diagnostic methods, such as the NSE test (8). Continuous research and findings related to NSE could have bolstered its reputation and applicability in pediatric conditions. The structure and emphasis of the pediatric healthcare system in Turkey might deviate from global norms, leading to distinct diagnostic approaches. The extent of knowledge and training among Turkish clinicians about NSE's efficacy might differ from their international counterparts, leading to discrepancies in testing rates. While certain countries might focus their research efforts on specific diagnostic methods or cancers, Turkey's emphasis on NSE might be a result of unique research trajectories. The presence or lack of other diagnostic tools in various countries can sway medical professionals' dependence on NSE tests.

Our research underscores the pivotal role of NSE within the sphere of tumor markers, particularly among pediatric populations. The fact that pediatric hematology and oncology clinics frequently employ NSE testing speaks volumes about its diagnostic value in children's malignancies.

The prevalence of NSE testing in pediatric domains within Turkey reveals significant insights about the nation's healthcare priorities. It's crucial to delve into the causes of this trend and juxtapose it with global practices to optimize diagnostic tactics and elevate patient care standards (9). Moreover, these findings can serve as a guidepost for other countries, facilitating mutual learning and fostering a cohesive approach towards leveraging NSE's potential.

Study Limitations

Several limitations should be considered when interpreting the findings of this study. First, the retrospective nature of the study and the use of retrospective data may introduce inherent limitations in terms of accuracy and precision. Second, the study's limited time frame restricts the generalizability of the results to a specific period. Third, the data were obtained from a specific region or institution, which may limit the generalizability of the findings to other geographic locations or healthcare settings. Fourth, the study did not fully analyze the relationship between the evaluated parameters and other clinical or laboratory findings, highlighting the need for further studies to determine the independent effect of NSE and its correlation with other variables. Fifth, the study focused solely on the use and effectiveness of NSE as a tumor marker, and comparative analyses with other tumor markers were not conducted. Finally, the study primarily evaluated test requests and results without considering other important clinical parameters such as treatment response or disease prognosis.

Conclusion

Our study highlights the prominent role of NSE as a valuable tumor marker in the diagnosis and assessment of neuroendocrine tumors and SCLC. The high diagnostic rate, frequent use in pediatric hematology and oncology clinics, and ability to detect cancer-related abnormalities distinguish NSE from other tumor markers. The findings of this study contribute to the existing body of knowledge and provide insights for clinicians and researchers in optimizing the clinical use of NSE in the management of these malignancies. Prospective studies in the future could provide further insights into the prognostic evaluation, treatment monitoring, and comparative effectiveness of NSE with other biomarkers.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ministry of Health of Turkey General Directorate of Health Information Systems (approval no: 95741342-020, date: 27.11.2019).

Informed Consent: Informed consent was obtained.

Peer-review: Internally and externally peer-reviewed

Authorship Contributions

Concept: S.B., Design: S.B., Data Collection or Processing: S.B., M.M.U., Analysis or Interpretation: S.B., M.M.U., Literature Search: S.B., M.M.U., Writing: S.B., M.M.U.

Conflict of Interests: The authors declare that they have no competing interests.

Funding: No funding has been received for this study.

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