



Research Article

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IDENTIFYING FACTORS ASSOCIATED WITH COGNITIVE IMPAIRMENT IN THYROID DISORDERS AND PREDICTION OF RISK USING MACHINE LEARNING APPROACH: A COMPREHENSIVE STUDY

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Abstract

Objectives: Thyroid disorders are a significant health concern in India and globally, being the second most common disease. Cognitive impairment associated with thyroid disorders is often neglected by healthcare providers, necessitating improved awareness and screening to identify neurocognitive changes in affected individuals. This study aimed to determine the prevalence of cognitive impairment in thyroid disorders and identify the associated risk factors. This study also predicted the risk of the development of cognitive impairment using a machine learning algorithm and was conducted in a tertiary hospital in South India.

Materials and Methods: A prospective observational study was conducted among 202 patients with thyroid disorders over six months. In order to achieve primary and secondary goals, tools such as the M-ACE questionnaire and XGBoost algorithm were used. Data were collected using a validated form and analyzed using standard statistical methods.

Results: Among the studied population, 29.21% were cognitively impaired, with an average M-ACE Score of 22.56 ± 2.62 . Age, duration of illness, BMI, comorbidities, and tobacco chewing were significant contributors when factors were analyzed for their association with cognitive impairment. A similar number of people with hypothyroidism and hyperthyroidism had a >75% risk of developing cognitive impairment in the near future.

Conclusion: This study revealed that thyroid disorders have significant effects on the cognitive status of individuals and were also successful in predicting future risk.

Keywords: Thyroid disorders, cognitive impairment, machine learning, XGBoost

Introduction

In the Indian population, endocrine disorders are prominent, and thyroid problems comprise a significant subset of these conditions.^{1,2} Globally, as in India, thyroid disorders are the second most common disease.³ The term "thyroid disorder" refers to a broad category of medical conditions that prevent the thyroid gland from producing the appropriate amount of hormones. The levels of triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH) in the blood indicate a spectrum of diseases that present as either hypo or hyperfunctioning of the thyroid gland.⁴ Thyroid hormone abnormalities may result from conditions affecting the thyroid gland itself (primary), pituitary conditions (secondary), or conditions affecting the hypothalamus (tertiary).²

Cognitive impairment is a frequently experienced problem among individuals with thyroid disorders, but it may be overlooked by healthcare providers if patients do not specifically report any changes in their neurocognitive functioning.^{5,6} Various factors, including sociodemographic variables (such as age, sex, marital status, educational status, and job status), comorbid medical conditions (such as hypertension, cardiovascular diseases, diabetes mellitus, and chronic kidney disease), behavioral factors such as tobacco chewing, drinking alcohol, and cigarette smoking, and disease-related factors such as duration of illness and thyroid hormone levels, contribute to future cognitive functions.⁵ In particular, low thyroid hormone is a common risk factor for the occurrence of cognitive impairment in aged females.⁷ According to studies determining the prevalence of cognitive impairment in thyroid disorders, the prevalence of cognitive impairment in hypothyroid patients was 27.3%.⁵ In hyperthyroidism, cognitive impairment was noticed as a common issue.⁸ People diagnosed with hyperthyroidism were having a major decline in their cognitive health compared to euthyroid patients.⁹ In hospitalized elderly hyperthyroid patients the prevalence of cognitive impairment was 52% with 33% dementia and 18% confusion.^{8,10}

Artificial intelligence (AI) is being used more frequently, which will probably alter how clinical evaluations and training are conducted. To ensure the potential of AI to improve medical care dramatically, doctors can collaborate in developing this technology for its application in medical care. This process generally entails gathering data, creating effective methods for using them, showing precise or approximate conclusions, and self-corrections/adjustments. AI is typically used to analyze machine learning to mimic human cognitive function. AI technology is used to conduct more accurate analyses and to achieve helpful interpretations.¹¹ This technology was used as a predictive model in this study.

This study aimed to determine the prevalence of cognitive impairment in patients with thyroid disease and identify the associated risk factors. Extreme gradient boosting (XGBoost) was also used to predict the risk of cognitive impairment.

Materials and Methods

A prospective study was conducted for six months in a research and training hospital with 202 diagnosed thyroid patients. The selected participants were of both genders, within the age range of 18 to 85 years. They displayed diverse clinical profiles, including comorbidities, educational levels, and social behaviors. Additionally, our sample had individuals from rural and urban areas, ensuring a comprehensive representation of thyroid patients across various demographic backgrounds.

Further, strict measures were taken to confirm that the selected participants had no prior history of seizure, epilepsy, stroke, schizophrenia, major depressive disorder, bipolar disorder, obsessive-compulsive disorder (OCD), brain tumor, head injury, or neurosurgery. Additionally, patients in critical condition, unable to communicate verbally or previously diagnosed with hearing impairments were excluded from the study. Notably, the study focused solely on diagnosed and under-treatment thyroid patients, meaning individuals with subclinical thyroid conditions were not part of our investigation. Therefore, the impact of subclinical conditions on cognitive health was not assessed in this study. This approach ensured a participant cohort with distinct clinical characteristics, providing a focused foundation for our study.

The data collection form was designed such that it contained separate sections for demographic details, patient history, lab values, and Mini Addrenbrooke's Cognitive Examination (M-ACE) scores. Patients' consent to participate in the study was obtained using an informed consent form in Kannada or English. First, the patient's demographic details were collected using a case sheet or direct patient interviews. The prevalence of cognitive impairment in thyroid patients was assessed using the M-ACE Questionnaire, and factors associated with cognitive impairment were collected, analyzed, and entered into an Excel sheet. Patients without any cognitive impairment were assessed for the risk of developing cognitive impairment using the XGBoost machine learning algorithm. XGBoost, which stands for extreme gradient boosting, is a machine learning algorithm. It is an optimized distributed gradient-boosting library designed to be highly efficient, flexible, and portable. It provides parallel tree boosting and is the leading machine-learning library for regression, classification, and ranking problems. It also has additional features for cross-validation and identification of important variables. The XGBoost model has the best combination of prediction performance and processing time compared to other algorithms.

The collected data were entered into Microsoft Excel Professional Plus 2016 and analyzed using the International Business Machine Statistical Presentation System Software (IBM SPSS) Version 25 for Windows. Categorical data are presented as frequencies and percentages. Quantitative data are represented as the mean and standard deviation (SD), and associations between categorical variables were assessed using the chi-

square test. Quantitative variables were compared using unpaired t-tests and analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant.

Results

A total of 202 thyroid patients with an average age of 45.92 years participated in this study, with a predominance of females (77.23%) (Table 1). In addition, 14.36% of patients admitted to engaging in substance abuse habits, including 5.94% of smokers, 5.45% of drinkers, and 2.97% of tobacco chewers. When the body mass index (BMI) was calculated, 50.99% of the population was identified as having a healthy weight, 33.66% was overweight, 9.90% was obese, and the remaining population was underweight. Comorbidities were present in 59.90% of the patients; the majority had diabetes (24.75%) and hypertension (22.77%), and the remainder had other comorbidities. Hypothyroidism (80.69%) was the major thyroid disorder among the participants, followed by hyperthyroidism (12.38%), and the rest were diagnosed with other thyroid conditions (6.93%). When the duration of illness was considered, 66.34% of the patients had thyroid disorders for ≤5 years (Table 2).

Table 1. Sociodemographic data of thyroid patients

Variables	Category	n	%
Age	18-28	34	16.83
	29-38	31	15.35
	39-48	49	24.26
	49-58	42	20.79
	59-68	33	16.34
	69-78	8	3.96
	79-88	5	2.48
Sex	Female	156	77.23
	Male	46	22.77
Residential area	Rural	91	45.05
	Urban	111	54.95
Educational status	≤ 8	64	31.68
	9 - 12	89	44.06
	> 12	49	24.26
Job-status	Employed	89	44.06
	Unemployed	107	52.97
	Retired	6	2.97

Table 2. Social behavior and clinical characteristics thyroid patients

Variables	Category	n	%
Social Habits	Smoking	12	5.94
	Alcohol	11	5.45
	Tobacco Chewing	6	2.97
	Nil	173	85.64
BMI	Underweight	11	5.45
	Healthy weight	103	50.99
	Overweight	68	33.66
	Obese	20	9.90
Comorbidities	Yes	121	59.90
	No	81	40.10
Thyroid disorders	Hypothyroidism	163	80.69
	Hyperthyroidism	25	12.38
	Other thyroid conditions	14	6.93
Duration of illness	≤5	134	66.34
	6-10	52	25.74
	11-15	13	6.44
	>15	3	1.48

Prevalence of cognitive impairment

In this study, the prevalence of cognitive impairment in patients with thyroid disorders was 29.21%. The severity of cognitive impairment was also tested according to the M ACE scores gained by the cognitively impaired patients, where 89.83% had mild cognitive impairment (MCI) and 10.17% had dementia. Of the 59 cognitively impaired patients, 72.88% had hypothyroidism, 15.25% had hyperthyroidism, and the rest had other thyroid conditions (Table 3).

Risk factors associated with cognitive impairment in thyroid patients

The chi-square test assessed many sociodemographic, social-behavioral, and clinical characteristics for their association with cognitive impairment. Among these factors, age ($p < 0.010$), duration of illness ($p = 0.030$), BMI ($p = 0.040$), tobacco chewing ($p = 0.040$), and comorbidities ($p = 0.002$) were significantly associated with cognitive impairment in patients with thyroid disorder (Table 4).

Table 3. Prevalence of cognitive Impairment

Variables	Category	n	(%)
Cognitive Impairment	Present	59	29.21
	Absent	143	70.79
Severity of Cognitive impairment	Mild	53	89.83
	Dementia	6	10.17
Cognitive impairment in thyroid disorders	Hypothyroidism	43	72.88
	Hyperthyroidism	9	15.25
	Other thyroid conditions	7	11.86

Table 4. Risk factors associated with cognitive impairment in thyroid patients

Variables	Cognitive Impairment No. of Cases (%)		Normal No. of Cases (%)		Chi-Square Test, p-value	
	n	%	n	%		
Age						
18-28	4	6.78	30	20.98	p<0.010	
29-38	10	16.95	21	14.69		
39-48	13	22.03	36	25.17		
49-58	10	16.95	32	22.38		
59-68	14	23.73	19	13.29		
69-78	5	8.47	3	2.10		
79-88	3	5.08	2	1.40		
Gender						
Male	15	25.42	31	21.68	p=0.564	
Female	44	74.58	112	78.32		
Education						
≤ 8	19	32.20	45	31.47	p=0.948	
9-12	25	42.37	64	44.76		
> 12	15	25.42	34	23.78		
Residential area						
Rural	29	49.15	62	43.36	p=0.452	
Urban	30	50.85	81	56.64		
Employment Status						
Employed	24	40.68	65	45.45	p=0.817	
Unemployed	33	55.93	74	51.75		
Retired	2	3.39	4	2.80		
Body Mass Index						
Underweight	6	10.17	5	3.50	p=0.040	
Healthy weight	22	37.29	81	56.64		
Overweight	24	40.68	44	30.77		
Obese	7	11.86	13	9.09		
Social Habits						
Tobacco Chewing	Yes	4	6.78	2	1.40	p=0.040
	No	55	93.22	141	98.60	
Smoking	Yes	3	5.08	9	6.29	p=0.740
	No	56	94.92	134	93.71	
Alcohol	Yes	2	3.39	9	6.29	p=0.410
	No	57	96.61	134	93.71	
Comorbidities						
Present	45	76.27	76	53.15	p=0.002	
Absent	14	23.73	67	46.85		
Duration of illness						
0-5	32	54.24	102	71.33	p=0.030	
6-10	20	33.90	32	22.38		
11-15	7	11.86	6	4.20		
> 15	0	0.00	3	2.10		

(Significant values are shown in bold)

Due to differences in the reference values of the thyroid function test, patients were segregated into age groups ≤ 60 years and >60 years to determine the relationship between thyroid hormones and cognitive impairment. When normal vs. below normal and normal vs. above normal levels of T3, T4, and TSH were compared individually, hypothyroidism was significantly associated with T3 (below normal), T4 (below and above normal), TSH (above normal), in patients with cognitive impairment aged ≤ 60 years, whereas T3 (below normal), T4 (below normal), and TSH (above normal) showed a significant association with cognitive impairment in patients aged >60 years ($p < 0.001$). Meanwhile, in hyperthyroidism, when comparison of normal vs. below normal and normal vs. above normal levels of T3, T4, and TSH were done individually, a significant association was found between T3 (above normal), T4 (above normal), TSH (below normal), in patients with cognitive impairment aged ≤ 60 years ($p < 0.001$) (Table 5).

Table 5. Thyroid function test

Hypothyroidism				
Age (in years)		T3 (in ng/dL) Mean (SD)	T4 (in µg/mL) Mean (SD)	TSH (in µIU/dL) Mean (SD)
≤ 60 years	Normal	0.98 (0.24)	6.94 (2.12)	2.88 (0.91)
	Below	0.29 (0.22)	1.42 (1.7)	0.05
	Unpaired t-test, p-value	$<0.001^*$	$<0.001^*$	-
	Normal	0.98 (0.24)	6.94 (2.12)	2.88 (0.91)
	Above	2.54	13.91(1.3)	17.56 (11.24)
	Unpaired t-test, p-value	-	$<0.001^*$	$<0.001^*$
> 60 years	Normal	0.92 (0.35)	7.29 (2.29)	4.82 (5.64)
	Below	0.2 (0.05)	2.54 (1.06)	-
	Unpaired t-test, p-value	$<0.001^*$	$<0.001^*$	-
	Normal	0.92 (0.35)	7.29 (2.29)	4.82 (5.64)
	Above	1.96	11.15	18.8(5.35)
	Unpaired t-test, p-value	-	-	$<0.001^*$
Hyperthyroidism				
Age (in years)		T3 (in ng/dL) Mean (SD)	T4 (in µg/mL) Mean (SD)	TSH (in µIU/dL) Mean (SD)
≤ 60 years	Normal	1.14 (0.28)	9.62 (0.55)	1.52 (0.91)
	Below	-	-	0.09(0.13)
	Unpaired t-test, p-value	-	-	$<0.001^*$
	Normal	1.14 (0.28)	9.62 (0.55)	1.52 (0.91)
	Above	4.18 (1.29)	19.7 (9.67)	-
	Unpaired t-test, p-value	$<0.001^*$	$<0.001^*$	-
> 60 years	Normal	1.84	-	2.25
	Below	0.11	1.03	0.19 (1.13)
	p-value	-	-	-
	Normal	1.84	-	2.25
	Above	7.25	15.6 (11.84)	-
	p-value	-	-	-

Risk prediction of cognitive impairment in thyroid patients with normal cognition

Cognitive impairment risk in thyroid patients with normal cognition during the study was predicted using the XGBoost machine learning algorithm (accuracy = 96.40%). Among 143 thyroid patients with normal cognition (M-ACE score > 25), 66 (46.15%) had a $\leq 25\%$ risk of cognitive impairment, 15 (10.49%) had a 26-50% risk, 34 (23.78%) had a 51-75% risk, and 27 (18.88%) had more than a 75% risk of developing cognitive impairment in the near future (Table 6). Table 6 also depicts the risk prediction of cognitive impairment in each thyroid disorder, where patients with hyperthyroidism (18.75%) and hypothyroidism (18.33%) showed almost similar results in more than 75% risk of developing cognitive impairment when compared to other thyroid conditions.

Discussion

The main focus of this study was to assess the relationship between thyroid disorders and cognitive impairment and to predict the future risk of cognitive impairment in thyroid patients. All participants were previously diagnosed with a thyroid condition and were 18 to 85 years old. Their compliance with inclusion and exclusion criteria was also verified. The overall prevalence of cognitive impairment in patients with thyroid disorders was approximately one-fourth (29.21%) of the total participants. Among those with cognitive impairments, nine out of ten (89.83%) exhibited mild cognitive impairment (with M-ACE scores ranging from 19-25), while the rest (10.17%) had dementia (with M-ACE scores of ≤ 18). Slightly over a quarter of the hypothyroid patients (26.38%) demonstrated cognitive difficulties, aligning with the findings of the study conducted by Mulat B et al., showing a prevalence of 27.3%.⁵ Conversely, approximately one-third (36.00%) of hyperthyroid patients demonstrated cognitive impairment.

After considering sociodemographic data, social behavior, and clinical factors associated with cognitive impairment, increased age, increased duration of illness, abnormal BMI, tobacco chewing, and comorbidities were found to be significantly linked. These findings were supported by the study conducted by Mulat B et al.⁵

Regarding sociodemographic variables, increased age was significantly associated with cognitive impairment, which agreed with the study conducted by Osterweil et al., which demonstrated a significant correlation between age and cognitive impairment in adult hypothyroid patients.¹² According to Zhang et al., age-dependent thyroid insufficiency encourages exosomal transfer of peripheral ApoE4 into the brain, which causes cognitive impairment.¹³ Other factors such as gender, education, residential area, and employment status were not significantly associated with cognitive impairment. Behavioral variables, such as social habits (tobacco chewing, smoking, and alcohol consumption) and sleep status, were also analyzed, causing a significant association between tobacco chewing and cognitive impairment. This aligns with the notion of the

study by Mohammed T et al., except for smoking and alcohol.¹⁴ Disease-related factors such as increased duration of illness and abnormal T3 were positively associated with cognitive impairment, which resembles the results of Mulat B et al.⁵ Various studies collectively imply that there may be a continuum describing the relationship between thyroid function and cognition, where cognitive dysfunction is caused by either increased or decreased thyroid hormone concentrations.¹⁵ Some evidence shows that mild hypothyroidism causes reduced cerebral blood flow in the areas of the brain that control attention, motor speed, memory, and visuospatial processing.¹⁶ In cases of clinical hypothyroidism, high TSH levels may also reduce cerebral blood flow and glucose metabolism.^{17,18} Patients with hyperthyroidism were found to have higher levels of oxidative stress, lower levels of antioxidant metabolites, and increased levels of thyroid hormonal exposure, leading to increased neuronal death.¹⁹

While our findings underscore the significant impact of hypo- and hyperthyroidism on cognitive decline, it is important to consider the broader context presented in the study by van Vliet et al. Their comprehensive analysis, involving a large participant cohort from 23 cohorts, found no significant association between subclinical thyroid dysfunction and cognitive function, cognitive decline, or dementia. While our results affirm the influence of hypo- and hyperthyroidism on cognitive decline, it is evident that further research is warranted to fully elucidate the complex interplay between thyroid function and cognitive health. Additionally, the implications of these findings for clinical practice necessitate a careful reevaluation of existing guidelines, particularly those advocating for the screening of subclinical thyroid dysfunction to prevent cognitive decline or dementia. That underscores the need for a balanced and evidence-based approach to managing thyroid disorders in the context of cognitive health.²⁰ Additionally, a meta-analysis by Ye Y et al. implies that comorbidities may influence the association between hypothyroidism and cognitive dysfunction.²¹ When comorbidities were not considered, no significant link was found. However, upon accounting for comorbidities related to vascular disease, hypothyroidism was associated with a lower risk of cognitive dysfunction. This finding contradicts our study results. The authors also emphasize the need for further prospective observational studies to better understand this relationship in the future.²¹

James C et al. assessed the ability of a machine learning algorithm by comparing two existing models for dementia risk prediction (Brief Dementia Screening Indicator- BDSI and Cardiovascular Risk Factors, Aging, and Incidence of Dementia - CAIDE) with four different machine learning algorithms (Logistic Regression-LR, Support Vector Machine-SVM, Random Machine-RF, XGBoost), which proved that machine learning algorithms were superior, in which XGBoost was the most powerful and accurate machine learning approach.²² Thus, our study used the XGBoost machine learning algorithm with an accuracy of 96.40% for risk prediction.

A risk assessment of 143 patients with no cognitive impairment (NCI) for cognitive impairment was performed, in which 18.88% had a more than 75% risk of developing cognitive impairment. Patients with hyperthyroidism

(18.75%) and hypothyroidism (18.33%) showed similar results in terms of more than 75% risk of developing cognitive impairment compared to other thyroid conditions. Thyroid hormones have many target genes that are important for many brain functions, and numerous genes acquire important functions in the nervous system, such as T3, which plays a crucial role in cerebral cortex development.^{23,24} One such example of a gene regulated by thyroid hormones is Reelin, which is produced by the RELN gene and has many functions, such as neuronal migration regulation, dendritic growth, dendritic spine formation, dendritic branching, and synaptic plasticity. Therefore, Reelin is related to many brain disorders, such as autism, depression, schizophrenia, and Alzheimer's disease.^{23,25} Moreover, brain-derived neurotrophic factor (BDNF) is involved in cognitive features. These levels are increased in the hippocampus, where the highest concentration is observed in the amygdala, cerebral cortex, and cerebellum. In the case of severe hypothyroidism due to the decrease in protein expression of BDNF, developmental and cognitive issues have been observed, in which memory is the one seen as most damaged.²⁶ The habit of loss in decision-making was observed in hyperthyroid patients, possibly because of metabolic disorders in the frontal cortex and limbic system.²⁷ The factors that can lead to an increased risk of developing cognitive problems in the future can be established from the data of this study. To the best of our knowledge, this is the first analysis to predict the risk of cognitive impairment in thyroid patients using the XGBoost machine learning algorithm.

While our study offers crucial insights into the link between thyroid disorders and cognitive function and enhances the awareness about the overlooked aspect of cognitive health in thyroid patients, it's important to acknowledge some limitations. Though carefully chosen, the sample size may be considered modest, particularly when accounting for potential subgroup variations within the population. Additionally, excluding participants with specific medical histories may limit the generalizability of our findings, and the potential presence of undiagnosed medical conditions could have influenced our outcomes. Focusing on diagnosed patients receiving treatment may not fully represent those with milder thyroid conditions, including subclinical thyroid conditions. Combining the M-ACE test with ACE III and other cognitive assessment tools could strengthen our results. Finally, we could not capture long-term trends due to the six-month duration and cross-sectional nature. Despite these constraints, our study provides a foundational insight into this critical area of research.

In conclusion, thyroid dysfunction is a key factor in the development of cognitive impairment. Significant risk factors for the development of cognitive impairment in patients with thyroid disease include advanced age, prolonged disease duration, abnormal BMI, comorbidities, altered T3, T4, and TSH levels, and tobacco chewing. Therefore, early screening of cognitive status in patients with the abovementioned risk factors is advised to ensure timely diagnosis, prevent disease progression, reduce financial burden, and improve quality of life.

Moreover, as AI programs continue to find their place in clinical practice, it is foreseeable that AI will take on a prevalent and influential role in evaluating cognitive function among patients with thyroid disorders. Thus, the incorporation of AI technologies holds the potential to streamline and enhance the accuracy of cognitive assessments, revolutionizing the way of diagnosis and management of cognitive impairment in this patient population.

Ethical Considerations: The study received ethical clearance from the BPC Institutional Ethics Committee on Human Subjects, identified by reference number BPC/IEC/75/2021-22.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Nagarkar R, Roy S, Akheel M, Palwe V, Kulkarni N, Pandit P. Incidence of thyroid disorders in India: An institutional retrospective analysis. *Int J Dent Med Specialty*. 2015;2(2):19-23 (doi: 10.5958/2394-4196.2015.00012.6).
2. Singh A, Purani C, Mandal A, Mehariya KM, Das RR. Prevalence of thyroid disorders in children at a tertiary care hospital in Western India. *J Clin Diagn Res*. 2016;10(2):1-4 (doi: 10.7860/JCDR/2016/16315.7189).
3. Bose A, Sharma N, Hemvani N, Chitnis DS. A hospital based prevalence study on thyroid disorders in Malwa region of Central India. *Int J Curr Microbiol App Sci*. 2015;4(6):604-11.
4. Vissenberg R, Manders VD, Mastenbroek S, et al. Pathophysiological aspects of thyroid hormone disorders/thyroid peroxidase autoantibodies and reproduction. *Hum Reprod Update*. 2015;21(3):378-87 (doi: 10.1093/humupd/dmv004).
5. Mulat B, Ambelu A, Yitayih S, et al. Cognitive impairment and associated factors among adult hypothyroid patients in referral hospitals, Amhara region, Ethiopia: Multicenter cross-sectional study. *Neuropsychiatr Dis Treat*. 2021;17:935-43 (doi: 10.2147/NDT.S299840).
6. Rajesh CH L, Reddy Endreddy A, Shaik S, S S. A study of cognitive dysfunctions in patients with thyroid disorders. *Int J Med Res Rev*. 2017;5(11):933-42 (doi: 10.17511/IJMRR.2017.111.03).
7. Ribeiro FS, de Oliveira Duarte YA, Santos JLF, Leist AK. Changes in prevalence of cognitive impairment and associated risk factors 2000-2015 in Sao Paulo, Brazil. *BMC Geriatr*. 2021;21(1):609 (doi: 10.1186/s12877-021-02542-x).
8. Rubin DI. Neurologic manifestations of hyperthyroidism and Graves' disease [Internet]. 2022; <https://www.medilib.ir/uptodate/show/4836> [Accessed: 03.06.2022].
9. Yudiarto FL, Muliadi L, Moeljanto D, Hartono B. Neuropsychological findings in hyperthyroid patients. *Acta Med Indones*. 2006;38(1):6-10.
10. Martin FIR, Deam DR. Hyperthyroidism in elderly hospitalised patients: Clinical features and treatment outcomes. *Med J Aust*. 1996;164(4):200-3 (doi: 10.5694/j.1326-5377.1996.tb94135.x).
11. Das S, Dey R, Nayak AK. Artificial intelligence in pharmacy. *Indian J Pharm Educ Res*. 2021;55(2):304-18 (doi: 10.5530/ijper.55.2.68).
12. Osterweil D, Syndulko K, Cohen SN, et al. Cognitive function in non-demented older adults with hypothyroidism. *J Am Geriatr Soc*. 1992;40(4):325-35 (doi:10.1111/j.1532-5415.1992.tb02130.x).
13. Zhang M, Gong W, Zhang D, et al. Ageing related thyroid deficiency increases brain-targeted transport of liver-derived ApoE4-laden exosomes leading to cognitive impairment. *Cell Death Dis*. 2022;13(406):1-13 (doi: 10.1038/s41419-022-04858-x).

14. Muhammad T, Govindu M, Srivastava S. Relationship between chewing tobacco, smoking, consuming alcohol and cognitive impairment among older adults in India: a cross-sectional study. *BMC Geriatr.* 2021;21(85):1-14 (doi: 10.1186/s12877-021-02027-x).
15. Begin ME, Langlois MF, Lorrain D, Cunnane SC. Thyroid function and cognition during aging. *Curr Gerontol Geriatr Res.* 2008;2008:1-11 (doi: 10.1155/2008/47486824).
16. Krausz Y, Freedman N, Lester H, et al. Regional cerebral blood flow in patients with mild hypothyroidism. *J Nucl Med.* 2004;45(10):1712-5.
17. Constant EL, de Volder AG, Ivanoiu A, et al. Cerebral blood flow and glucose metabolism in hypothyroidism: A positron emission tomography study. *J Clin Endocrinol Metab.* 2001;86(8):3864-70 (doi: 10.1210/jcem.86.8.7749).
18. Duntas LH, Maillis A. Hypothyroidism and depression: salient aspects of pathogenesis and management. *Minerva Endocrinol.* 2013;38(4):365-77.
19. Hu Y, Wang ZC, Guo QH, Cheng W, Chen YW. Is thyroid status associated with cognitive impairment in elderly patients in China?. *BMC Endocr Disord.* 2016;(1):1-7 (doi: 10.1186/s12902-016-0092-z).
20. van Vliet NA, van Heemst D, Almeida OP, et al. Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. *JAMA Intern Med.* 2021;181(11):1440-50 (doi:10.1001/jamainternmed.2021.5078).
21. Ye Y, Wang Y, Li S, Guo J, Ding L, Liu M. Association of Hypothyroidism and the Risk of Cognitive Dysfunction: A Meta-Analysis. *J Clin Med.* 2022; 11(22):6726 (doi: 10.3390/jcm11226726).
22. James C, Ranson JM, Everson R, Llewellyn DJ. Performance of machine learning algorithms for predicting progression to dementia in memory clinic patients. *JAMA netw open.* 2021;4(12):e2136553 (doi: 10.1001/jamanetworkopen.2021.36553).
23. Khaleghzadeh-Ahangar H, Talebi A, Mohseni-Moghaddam P. Thyroid disorders and development of cognitive impairment: A review study. *Neuroendocrinology.* 2022;112(9):835-44 (doi: 10.1159/000521650).
24. Bernal J. Thyroid hormone regulated genes in cerebral cortex development. *J Endocrinol.* 2017;232(2):R83-97 (doi: 10.1530/JOE-16-0424).
25. Jossin Y. Reelin functions, mechanisms of action and signaling pathways during brain development and maturation. *Biomolecules.* 2020;10(6):964 (doi: 10.3390/biom10060964).
26. Madhusudhan U, M K, Singaravelu V, Ganji V, John N, Gaur A. brain-derived neurotrophic factor-mediated cognitive impairment in hypothyroidism. *Cureus.* 2022;14(4):e23722 (doi: 10.7759/cureus.23722).
27. Yuan L, Tian Y, Zhang F, et al. Decision-making in patients with hyperthyroidism: A neuropsychological study. *PLoS One.* 2015;10(6):e0129773 (doi: 10.1371/journal.pone.0129773).