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Neutrophil / Lymphocyte ratio in frontotemporal dementia

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Abstract

Frontotemporal dementia (FTD) is a progressive neurodegenerative disease characterized by behavioral, cognitive, and speech disorders. The neutrophil/lymphocyte ratio (NLR), an inexpensive and easily calculated indicator of systemic inflammation, has been evaluated as a biomarker in many neurodegenerative diseases. Our study aimed to investigate the relationship between NLR and FTD and to demonstrate its potential diagnostic value. Forty-eight FTD patients and 48 healthy controls were retrospectively analyzed. Demographic, biochemical, hematological, and cognitive outcomes of the participants were compared. ANCOVA and logistic regression analyses were performed, and principal component analysis (PCA) was applied to assess multivariate discrimination. NLR levels were found to be significantly higher in the FTD group than in the control group (median 4.825 vs. 1.63; $p<0.001$). This significant difference remained significant after adjustment for variables such as age, body mass index, hemoglobin, liver enzymes, glucose, blood urea nitrogen (BUN), and platelet count. Although logistic regression analysis yielded a high odds ratio (Exp(B) = 10.441) for NLR, statistical significance was not achieved. This could be explained by the limited sample size. Furthermore, NLR was positively correlated with glucose, BUN, AST, and ALT, and negatively correlated with hemoglobin and BMI. PCA analysis revealed NLR as the strongest variable distinguishing between the groups. Our study findings suggest a possible association between FTD and systemic inflammation. NLR is not yet a diagnostic marker alone, but when used in conjunction with clinical and radiological findings, it may be useful in the early diagnosis and risk stratification of FTD. Larger and more advanced studies are needed to confirm our results and clarify their clinical significance.

Keywords: Frontotemporal dementia, neutrophil-to-lymphocyte ratio, systemic inflammation, biomarker, alzheimer's

Introduction

Dementia manifests as a progressive decline in cognitive function and is a significant public health problem due to its personal, social, and economic burden. Its increasing prevalence and widespread community involvement have made dementia a major global health problem. According to the World Health Organization, as of 2023, there will be approximately 55 million people with dementia worldwide, with approximately 10 million new cases diagnosed each year. Dementia is a leading cause of death worldwide and a significant cause of dependency among older adults. The economic cost of this pathology was estimated at approximately $1.3 trillion in 2019 [1].

Frontotemporal dementia (FTD) is a clinically heterogeneous group of neurodegenerative disorders characterized by progressive degeneration of the frontal and temporal lobes, often involving subcortical structures [2-4]. Typical symptoms of FTD include behavioral and personality changes, functional impairments, language impairments, psychiatric problems, and motor abnormalities. Microscopically, gliosis, microvacuolization, and synapse and neuron damage are observed [5]. As the disease progresses, degeneration spreads to the hippocampus, basal ganglia, thalamus, and white matter, and the extent of spread to these regions correlates with disease duration and clinical severity [6]. In FTD, a relatively rare disease (estimated prevalence 15-22 per 100,000 individuals and incidence 2.7-4.1 per 100,000 individuals), small population studies can also provide information regarding the clinical profile, diagnostic markers, and pathophysiological basis [7].

In recent years, the neutrophil-to-lymphocyte ratio (NLR), an easily calculated marker obtained from routine complete blood

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count tests, has been investigated as a potential indicator of systemic inflammation. This ratio is calculated by dividing the number of neutrophils by the number of lymphocytes, and its relationship with many diseases has been investigated. Elevated NLR has been reported in many pathologies, including Alzheimer's disease [8], COVID-19 prognosis [9], irritable bowel syndrome [10], type II diabetes mellitus [11], diabetic nephropathy [12], Parkinson's disease [13], and various malignancies [14]. As a marker reflecting the balance between innate and adaptive immunity, NLR is thought to be an indicator of immune dysregulation and inflammatory response. Since its association with many neurological diseases (Alzheimer's disease, Parkinson's disease) has been strongly demonstrated in many studies, the association between FTD and NLR is also very likely.

FTD can mimic various psychiatric disorders, making early and accurate diagnosis difficult. Consequently, numerous studies have focused on elucidating the clinical, laboratory, epidemiological, genetic, and neuropathological features of FTD to improve diagnostic accuracy [15]. Emerging evidence also suggests that both systemic and neuroinflammation play a role in FTD pathogenesis [16]. While some studies have not found statistically significant differences in NLR and other inflammatory markers across various dementia subtypes [17], others, such as the Framingham Heart Study, have shown that elevated NLR may predict future dementia risk [18,19]. Furthermore, higher NLR levels have been observed in patients with Alzheimer's and Parkinson's disease compared to healthy controls [20,21]. These findings highlight the need for further investigation of the relationship between inflammation and neurodegeneration.

While numerous studies demonstrating these relationships exist, studies specifically investigating NLR in frontotemporal dementia are limited. In our study, we aimed to investigate the potential relationship between the neutrophil-to-lymphocyte ratio and FTD and to assess whether NLR has diagnostic significance.

Material and Methods

Study setting and study population

Our study included 48 patients aged 18 years and older who presented to the Neurology Clinic of Ankara Etlik City Hospital between January 2023 and December 2024 and were diagnosed with frontotemporal dementia. The most commonly used criteria for diagnosing FTD were defined by Rascovsky et al. in 2011. According to these criteria, the diagnosis of behavioral variant FTD (bvFTD) is classified as possible, probable, or definite. Probable bvFTD is also diagnosed with significant impairment in daily living activities and typical atrophy or hypometabolism in the frontal and/or anterior temporal regions on neuroimaging (MRI or PET). A definitive diagnosis is made only by pathological examination (biopsy, autopsy) or by detecting mutations (MAPT, GRN, and C9orf72) [22]. Therefore, in neurological practice, patients are classified as probable or probable, and a definitive diagnosis is rarely made. In our study, when the clinical features and radiological findings of the patient group were evaluated together, a diagnosis of "probable FTD" was made according to Rascovsky's criteria. Those younger than 18 years, those with other types of dementia, and those with incomplete medical data were excluded from the study. Forty-eight individuals who applied to the neurology clinic, had no history of drug use, were not diagnosed with dementia, did not have a chronic disease, had normal physical examination and laboratory findings, and were not prescribed medication were included in our study as controls. Age, gender, blood pressure, body mass index, complete blood count parameters (neutrophils, lymphocytes, neutrophil/lymphocyte ratio), routine biochemistry tests, and other clinical information were retrospectively analyzed. The study protocol was approved by the Etlik City Hospital Ethics Committee (date: 09.04.2025; acceptance Number: 2025-0288).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY), Analyse-it for Microsoft Excel (Analyse-it Software, Ltd., Leeds, UK), and the MetaboAnalyst 6.0 platform (https://www.metaboanalyst.ca) for multivariate visualization. Normal distribution of continuous data was tested with Shapiro Wilks. The Mann-Whitney U test was used to determine the difference between groups of non-normally distributed data, and continuous data were expressed as median (25–75% interquartile range). The Chi-square test was used in categorical data analysis.

Logistic regression analysis was used to evaluate the relationship between individual biomarkers (e.g., NLR) and group status (FTD vs. control). Model fit was assessed with the Hosmer–Lemeshow test, and odds ratios (ORs) with 95% confidence intervals were reported. To control for potential confounding variables, an analysis of covariance (ANCOVA) was performed using NLR as the dependent variable and group (FTD vs. control) as the fixed factor. Covariates included age, body mass index (BMI), hemoglobin (HGB), platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, and blood urea nitrogen (BUN) levels. The adjusted group effect was considered statistically significant at $p < 0.05$. Multivariate data structure and clustering patterns were further evaluated by principal component analysis (PCA), performed via MetaboAnalyst 6.0. Autoscaling was applied prior to PCA. The results were presented as pairwise density plots, biplots, 2D scores plots, and 3D PCA scatter plots to visualize group separation and variable contributions. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

Sample size estimation was performed using G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany). Based on an expected effect size (Cohen's d) of 0.85 derived from the study by Sjögren et al. [23], which demonstrated

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elevated inflammatory activity in patients with. Minimum of 74 subjects (37 per group) was required to achieve 95% power (1-β = 0.95) at a 5% significance level (α = 0.05). To increase statistical robustness and account for potential variability, we included 96 participants in total, with 48 FTD patients and 48 age- and sex-matched healthy controls.

Results

When we examined the gender distribution in the FTD patient group and the healthy control group, no statistically significant difference was found. In terms of age, the FTD group tended to be older than the control group, but the difference was not statistically significant. Cognitive assessment was performed only in the FTD group. The results showed significant impairments in general cognitive function and in subscores of memory, orientation, and attention/calculation. As expected, not all participants in the healthy control group had diabetes or hypertension, although both conditions were present in all individuals with FTD.

Regarding BMI, a statistically significantly lower median value was observed in the FTD patient group compared to the healthy group. Liver enzyme activities (ALT and AST) were found to be significantly higher in the FTD group. Furthermore, higher blood glucose and BUN levels were observed in the FTD patients, reflecting possible metabolic and renal changes. No significant difference was found in platelet counts between the groups (Figure 1). Hematological analysis revealed that hemoglobin and lymphocyte levels were significantly lower in the FTD group, while neutrophil counts and neutrophil/lymphocyte ratio were significantly higher (Figure 2). All results were summarized in Table 1.

Table 1. Demographic, clinical, cognitive, and biochemical characteristics of individuals with frontotemporal dementia and healthy controls

Parameter	Category	Healthy Control (N=48)	FTD (N=48)	P value
Gender	**Female**	24 (49%)	25 (51%)	0.835
	Male	24 (51%)	23 (48.9%)	
DM	**Absent**	48 (57.8%)	35 (42.2%)	ND
	Present	0 (0)	13 (100)	
HT	**Absent**	48 (57.8%)	35 (42.2%)	ND
	Present	0 (0)	13 (100)	
MRI Stage	**Stage 1**	-	20 (45.9%)	ND
	Stage 2	-	17 (35.4%)	
	Stage 3	-	9 (18.8%)	
Mini-Mental State Examination		-	15.5 (10.5–21)	ND
Memory Subscore		-	1 (0–2)	ND
Orientation Score		-	5 (4–8)	ND
Attention and Calculation Score		-	1 (0–3)	ND
Age (year)		57 (53–63)	60 (55–64)	0.05
BMI (kg/m²)		28.7 (25.6–31.9)	26.4 (23.1–28.1)	**0.001**
HGB (g/L)		14 (13.5–15)	13 (11–15)	**0.001**
Platelet (x109/L)		306 (219–337)	266 (207–308)	0.086
ALT (U/L)		19.0 (10.5–31.0)	27.0 (19.0–44.5)	**0.001**
AST (U/L)		20.0 (11.0–30.0)	40.0 (21.0–56.5)	**0.001**
Glucose (mg/dL)		88.0 (82.5–92.0)	107 (93.0–129)	**0.001**
BUN (mg/dL)		32 (27–41)	44 (35–56)	**0.001**
Neutrophil (x109/L)		5.12 (3.91–5.85)	7.01 (5.21–9.30)	**0.001**
Lymphocyte (x109/L)		3.05 (2.40–3.60)	1.45 (0.95–2.01)	**0.001**
NLR		1.63 (1.34–1.91)	4.825 (2.89–8.74)	**0.001**

DM: Diabetes Mellitus; HT: Hypertension; MRI: Magnetic Resonance Imaging; BMI: Body Mass Index; HGB: Hemoglobin; ALT and AST: Alanine Aminotransferase and Aspartate Aminotransferase, respectively; BUN: Blood Urea Nitrogen; NLR: Neutrophil-to-Lymphocyte Ratio; FTD: Frontotemporal Dementia; and ND: Not detected.

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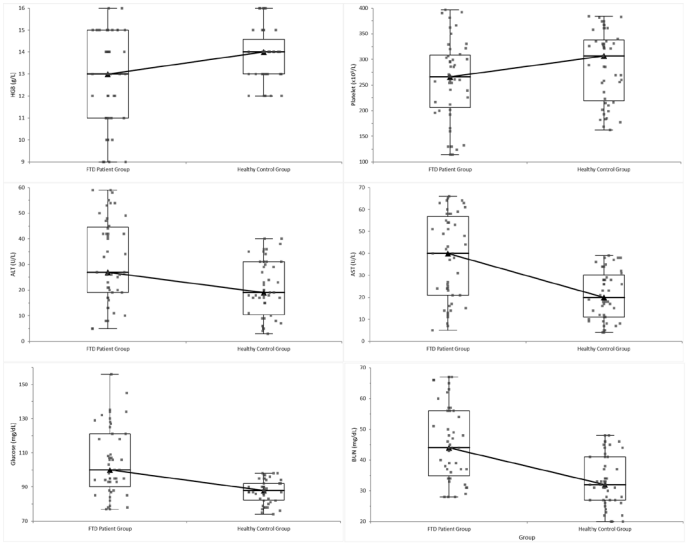

Figure 1. Comparison of HGB, platelet count, ALT, AST, glucose, and BUN levels between the FTD and healthy control groups

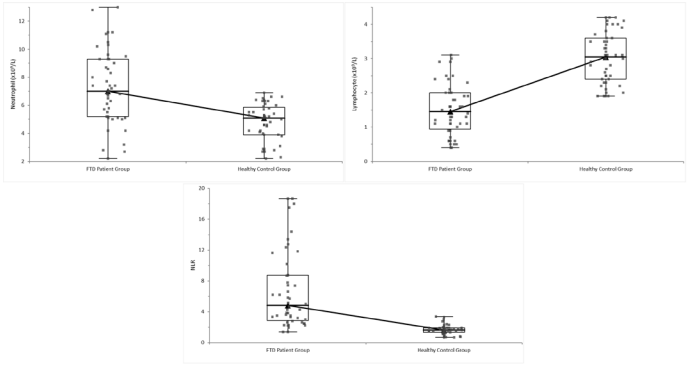

Figure 2. Comparison of neutrophil count, lymphocyte count, and neutrophil-to-lymphocyte ratio NLR between the ftd and healthy control groups

In the healthy control group, most biochemical and hematological parameters showed weak or nonsignificant associations. A statistically significant negative correlation was observed between AST and glucose levels, indicating a potential inverse relationship between hepatic enzyme activity and glucose concentration in this cohort. Additionally, BUN was positively correlated with platelet count. Strong inter-relationships were identified among inflammatory markers: neutrophil count showed a strong positive correlation with NLR and a moderate positive correlation with lymphocyte count, while lymphocyte count was inversely correlated with NLR. These findings are consistent with the mathematical structure of NLR, which reflects the balance between neutrophil and lymphocyte levels (Table 2).

In the FTD group, several statistically significant correlations were observed between laboratory variables and cognitive performance. Hemoglobin levels were positively correlated with overall cognitive status, as measured by the Mini-Mental State Examination (MMSE), and with orientation and attention/calculation scores. Conversely, it was negatively correlated with the memory subscore, suggesting domain-specific associations. Platelet count was negatively correlated with both BUN and orientation performance. AST levels showed a negative association with BUN, and a moderate inverse correlation with the orientation score. Lymphocyte count demonstrated a negative correlation with the memory subscore and a positive association with the orientation score. However, glucose, ALT, and NLR did not exhibit significant correlations with any cognitive domains. Strong intercorrelations were found among the cognitive variables themselves. MMSE was highly correlated with all three cognitive subscores—memory, orientation, and attention/calculation—supporting their internal consistency in reflecting cognitive function within the FTD population (Table 3). In addition to subgroup-specific correlation analyses, an overall correlation heatmap was generated to explore the general interaction patterns across all individuals (Figure 3). NLR demonstrated statistically significant correlations with several biochemical and hematological parameters across all participants (N=96). As expected, NLR was strongly and positively correlated with neutrophil count (r=0.753, p<0.001), and strongly and negatively correlated with lymphocyte count (r=–0.844, p<0.001), reflecting the ratio's direct dependence on these two parameters.

In addition, NLR showed a moderate positive correlation with BUN (r=0.527, p<0.001), glucose (r=0.452, p<0.001), AST (r=0.218, p=0.033), and ALT (r=0.261, p=0.010), suggesting potential links between systemic inflammation and metabolic or hepatic alterations. Conversely, NLR was negatively correlated with HGB (r=–0.342, p=0.001) and BMI (r=–0.264, p=0.009), and weakly negatively correlated with age (r=–0.242, p=0.017), which may reflect inflammation-related hematological and anthropometric changes (Figure 3).

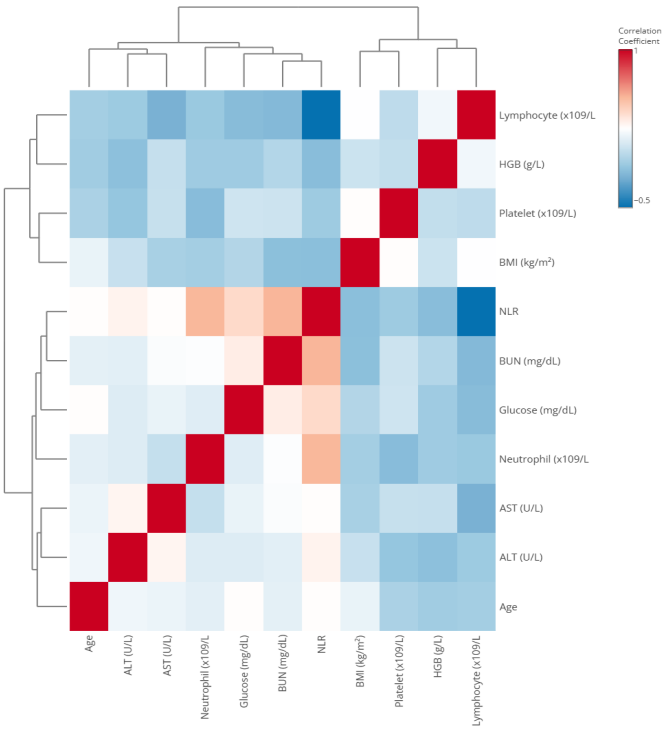

Figure 3. Hierarchical clustered heatmap showing pairwise spearman correlation coefficients among biochemical and hematological parameters across all participants (FTD+healthy control; N=96). Positive correlations are shown in red and negative correlations are shown in blue. the color intensity reflects the strength of correlation. clustering was performed using average linkage based on the euclidean distance

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Table 2. Spearman correlation coefficients among biochemical and hematological parameters in the healthy control group (N=48)

Spearman's rho		Age (year)	BMI	HGB (g/L)	Platelet (x109/L)	ALT (U/L)	AST (U/L)	Glucose (mg/dL)	BUN (mg/dL)	Neutrophil (x109/L)	Lymphocyte (x109/L)	NLR
Spearman's rho												
Age (year)	r	1	0.161	0.116	0.004	0.049	0.060	0.192	-0.270	0.146	0.005	0.039
	p	.	0.275	0.432	0.978	0.741	0.687	0.192	0.064	0.323	0.972	0.792
	N		48	48	48	48	48	48	48	48	48	48
BMI (kg/m²)	r		1	-0.075	0.057	0.113	0.021	0.106	-0.061	0.010	0.111	-0.028
	p		.	0.612	0.703	0.443	0.888	0.471	0.680	0.947	0.454	0.848
	N			48	48	48	48	48	48	48	48	48
HGB (g/L)	r			1	-0.060	0.186	-0.021	-0.203	-0.288*	-0.003	0.232	-0.229
	p			.	0.684	0.206	0.889	0.166	0.047	0.983	0.112	0.118
	N				48	48	48	48	48	48	48	48
Platelet (x10⁹/L)	r				1	-0.207	-0.044	0.250	0.324*	0.084	-0.132	0.199
	p				.	0.157	0.768	0.086	0.025	0.571	0.370	0.175
	N					48	48	48	48	48	48	48
ALT (U/L)	r					1	0.269	-0.159	-0.066	-0.273	-0.244	-0.017
	p					.	0.065	0.280	0.657	0.060	0.094	0.911
	N						48	48	48	48	48	48
AST (U/L)	r						1	-0.379**	0.179	-0.099	-0.226	0.035
	p						.	0.008	0.223	0.503	0.122	0.811
	N							48	48	48	48	48
Glucose (mg/dL)	r							1	-0.007	0.061	0.052	0.161
	p							.	0.965	0.681	0.724	0.274
	N								48	48	48	48
BUN (mg/dL)	r								1	-0.087	-0.265	0.144
	p								.	0.555	0.068	0.329
	N									48	48	48
Neutrophil (x10⁹/L)	r									1	0.140	0.646**
	p									.	0.341	0.000
	N										48	48
Lymphocyte (x10⁹/L)	r										1	-0.592**
	p										.	0.000
	N											48

a. Groups: Healthy control

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Table 3. Spearman correlation coefficients among biochemical, hematological, and cognitive parameters in the frontotemporal dementia (FTD) Group (N= 48)

	Spearman's rho		Age	BMI	HGB	Platelet	ALT	AST	Glucose	BUN	Neutrophil	Lymphocyte	NLR	MMSE	MS	OS	A/C
Spearman's rho	Age (year)	r	1	0.238	-0.076	-0.097	0.104	0.056	0.026	0.289*	0.080	-0.058	0.095	0.137	-0.113	0.126	0.187
		p	.	0.104	0.606	0.511	0.480	0.706	0.859	0.046	0.590	0.695	0.521	0.354	0.444	0.392	0.204
		N		48	48	48	48	48	48	48	48	48	48	48	48	48	48
	BMI (kg/m²)	r		1	-0.178	0.292*	0.183	0.026	-0.037	-0.062	0.041	-0.197	0.134	-0.051	0.178	-0.063	-0.105
		p		.	0.226	0.044	0.213	0.860	0.801	0.676	0.781	0.180	0.364	0.729	0.227	0.670	0.477
		N			48	48	48	48	48	48	48	48	48	48	48	48	48
	HGB (g/L)	r			1	-0.042	-0.180	0.241	0.052	0.106	0.093	-0.029	0.034	0.456**	0.318*	0.418**	0.289*
		p			.	0.779	0.220	0.099	0.727	0.472	0.531	0.845	0.820	0.001	0.028	0.003	0.046
		N				48	48	48	48	48	48	48	48	48	48	48	48
	Platelet (x109/L)	r				1	-0.057	0.209	0.055	-0.013	-0.364*	-0.050	-0.174	-0.217	-0.009	-0.311*	-0.092
		p				.	0.702	0.154	0.712	0.928	0.011	0.737	0.237	0.138	0.954	0.031	0.532
		N					48	48	48	48	48	48	48	48	48	48	48
	ALT (U/L)	r					1	0.031	0.042	-0.068	-0.066	-0.040	0.004	-0.037	0.143	-0.042	0.084
		p					.	0.834	0.776	0.644	0.656	0.787	0.981	0.801	0.331	0.776	0.571
		N						48	48	48	48	48	48	48	48	48	48
	AST (U/L)	r						1	0.006	-0.212	-0.285*	0.175	-0.348*	0.039	-0.192	0.005	0.034
		p						.	0.965	0.148	0.049	0.234	0.016	0.792	0.192	0.975	0.817
		N							48	48	48	48	48	48	48	48	48
	Glucose (mg/dL)	r							1	0.056	0.080	0.084	-0.014	-0.064	-0.058	-0.021	-0.165
		p							.	0.705	0.587	0.569	0.925	0.664	0.696	0.885	0.262
		N								48	48	48	48	48	48	48	48
	BUN (mg/dL)	r								1	0.268	-0.083	0.247	0.066	0.088	0.127	0.017
		p								.	0.066	0.574	0.091	0.657	0.552	0.390	0.906
		N									48	48	48	48	48	48	48
	Neutrophil (x10⁹/L)	r									1	-0.086	0.598**	0.112	-0.001	0.199	-0.089
		p									.	0.560	0.000	0.447	0.994	0.176	0.549
		N										48	48	48	48	48	48
	Lymphocyte (x10⁹/L)	r										1	-0.814**	-0.040	-0.301*	0.057	0.003
		p										.	0.000	0.785	0.038	0.702	0.983
		N											48	48	48	48	48
	NLR	r											1	0.049	0.212	0.014	-0.077
		p											.	0.740	0.148	0.926	0.601
		N												48	48	48	48
	Mini-Mental State Examination	r												1	0.434**	0.857**	0.704**
		p												.	0.002	0.000	0.000
		N													48	48	48
	Memory Subscore	r													1	0.379**	0.333*
		p													.	0.008	0.021
		N														48	48
	Orientation Score	r														1	0.601**
		p														.	0.000
		N															48

a. Groups = FTD

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A univariate analysis of covariance (ANCOVA) was conducted to evaluate whether the difference in neutrophil-to-lymphocyte ratio (NLR) between frontotemporal dementia (FTD) patients and healthy controls remained significant after adjusting for potential confounders, including age, body mass index (BMI), hemoglobin (HGB), platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), glucose, and blood urea nitrogen (BUN). The overall ANCOVA model was statistically significant ($F(9,86)=6.580$, $p<0.001$), indicating that a substantial proportion of the variance in NLR was explained by the model. The adjusted R^2 was 0.346, suggesting that approximately 35% of the variability in NLR could be accounted for by the included covariates and group membership. After adjusting for covariates, the effect of group (FTD vs. control) on NLR remained highly significant ($F(1,86)=19.378$, $p<0.001$), confirming that NLR was significantly elevated in the FTD group independent of other biochemical parameters. Covariates, including age (p=0.480), BMI (p=0.680), HGB (p=0.564), platelet count (p=0.776), ALT (p=0.858), AST(p=0.057) glucose (p=0.854), and BUN (p= 0.203), did not exhibit statistically significant effects on NLR in the model. (Table 4).

Binary logistic regression analysis was performed to investigate the predictive value of NLR and related biochemical parameters for differentiating patients with FTD from healthy controls (Table 5).

Table 4. Results of Univariate ANCOVA assessing the effect of group (FTD vs. Control) on Neutrophil-to-Lymphocyte Ratio (NLR) after adjusting for age, BMI, hemoglobin, platelet count, ALT, AST, glucose, and BUN levels

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	717.151	9	79.683	6.580	0.000
Intercept	0.166	1	0.166	0.014	0.907
Age	6.097	1	6.097	0.503	0.480
BMI	2.068	1	2.068	0.171	0.680
HGB	4.067	1	4.067	0.336	0.564
Platelet	0.987	1	0.987	0.082	0.776
ALT	0.389	1	0.389	0.032	0.858
AST	71.246	1	71.246	5.883	0.057
Glucose	0.414	1	0.414	0.034	0.854
BUN	19.912	1	19.912	1.644	0.203
Group	234.662	1	234.662	19.378	**0.000**
Error	1041.419	86	12.110		
Total	3421.930	96			
Corrected Total	1758.571	95			

BMI: Body mass index; HGB: Hemoglobin; ALT and AST: Alanine aminotransferase and aspartate aminotransferase, respectively; BUN: Blood urea nitrogen

Table 5. Results of multivariate binary logistic regression assessing the predictive value of NLR and biochemical parameters for differentiating FTD patients from healthy controls

Parameter	B	Wald	Sig.	OR [Exp(B)]	95% CI for EXP(B)	
					Lower	Upper
Gender (1)	4.630	1.902	0.168	102.488	0.142	73813.631
Age (year)	-.020	.007	0.934	0.980	0.605	1.588
BMI (kg/m²)	-1.157	1.938	0.164	0.314	0.062	1.603
HGB (g/L)	-3.015	1.730	0.188	0.049	0.001	4.383
Platelet (x10⁹/L)	-0.026	0.834	0.361	0.975	0.922	1.030
ALT (U/L)	0.273	1.395	0.238	1.314	0.835	2.068
AST (U/L)	0.115	1.022	0.312	1.121	0.898	1.401
Glucose (mg/dL)	0.502	2.312	0.128	1.652	0.865	3.154
BUN (mg/dL)	0.257	1.709	0.191	1.293	0.880	1.902
NLR	2.346	1.147	**0.284**	**10.441**	0.143	763.771
Constant	8.139	0.066	0.798	3425.082		

Gender (1) indicate Female; 95%CI: 95% Confidence intervals

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The full model, which included age, gender, BMI, HGB, platelet count, ALT, AST, glucose, BUN, and NLR, was statistically significant, $\chi^2(10)=16.983$, $p<0.001$, indicating that the model was able to distinguish between FTD and control groups.

The model explained 93.5% of the variance in group status (Nagelkerke $R^2=0.935$) and correctly classified 100% of the cases. The Hosmer–Lemeshow goodness-of-fit test yielded a non-significant result ($\chi^2 = 0.588$, df = 8, p = 1.000), suggesting an excellent model fit to the data and no evidence of lack-of-fit.

Although NLR showed a positive association with FTD group membership (B=2.346, SE=2.190), this association did not reach statistical significance (p=0.284, Exp(B)=10.441, 95% CI:0.143–763.771). Similarly, none of the other covariates, including age, gender, BMI, and biochemical markers, were found to be independent predictors in the multivariate model (p>0.05 for all).

These findings indicate that although NLR showed a high point estimate for odds ratio, it was not a statistically significant predictor of FTD when adjusted for other potential confounders. The large confidence interval and lack of significance may be due to limited sample size or collinearity within the model. Therefore, future studies with larger cohorts and alternative modeling approaches (e.g., penalized regression) are warranted to explore the predictive value of NLR in FTD more robustly.

Principal Component Analysis (PCA) was conducted to explore potential group-based clustering patterns and underlying variance in the dataset. The first two principal components (PC1 and PC2) explained 57.6% and 40.8% of the total variance, respectively. The pairwise density plots (Figure 4A) demonstrated significant differences between FTD patients and healthy controls for PC1 through PC5 ($p < 0.05$), indicating meaningful multivariate separation. The PCA biplot (Figure 4B) showed that neutrophil-to-lymphocyte ratio (NLR) exhibited the strongest loading vector, aligning with the direction of separation between the two groups, followed by glucose and BUN levels. Variables such as ALT, AST, lymphocyte count, and BMI showed more moderate contributions. The PCA scores plot (Figure 4C) and 3D plot (Figure 4D) illustrated a partial yet notable clustering of FTD patients compared to healthy controls. While the groups were not completely linearly separable, the visualization suggested a latent multivariate structure distinguishing the two populations, with NLR emerging as a potentially influential biomarker.

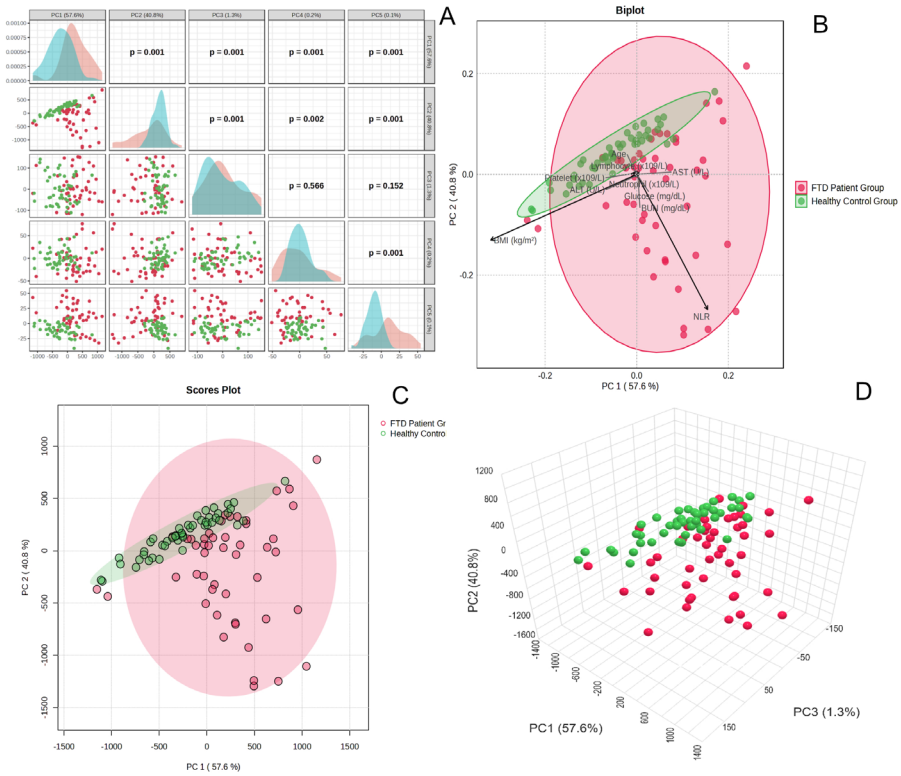

Figure 4. PCA for differentiating ftd patients and healthy controls. (A) Pairwise scatter plots and density distributions of the first five principal components (PC1 TO PC5). statistically significant group differences between ftd patients and healthy controls were evident in PC1, PC2, PC3, PC4, and PC5 ($P < 0.05$). (B) 2D PCA biplot showing the contribution of clinical variables to PC1 and PC2. The NLR showed the most prominent separation vector between the groups. (C) PCA score plot visualizing individual subject clustering across PC1 and PC2. A partial separation was observed between the FTD patients (RED) and healthy controls (GREEN). (D) 3D PCA plot based on PC1, PC2, and PC3, demonstrating multidimensional separation between the two groups

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Discussion

Our study showed that the neutrophil-to-lymphocyte ratio (NLR), a current marker of systemic inflammation, was significantly higher in patients with frontotemporal dementia (FTD) than in controls. Even after optimization for interfering factors such as age, body mass index, and various biochemical parameters, ANCOVA results revealed that NLR remained independently associated with FTD. This finding is consistent with recent evidence linking systemic inflammation to neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease [8,13,20], confirming our hypothesis that neuroinflammation may play an important role in the pathogenesis of FTD [16]. While NLR has been extensively studied in Alzheimer's disease, its role in FTD has not yet been fully established. Our findings add to the limited but growing literature suggesting that inflammatory markers may have diagnostic or prognostic value in FTD. In particular, the increased neutrophil count and the significant decrease in lymphocyte count in the FTD group may reflect a mechanism in the innate and adaptive immune system, which has previously been suggested to play a role in neurodegenerative processes [15,16,19].

Although the logistic regression model demonstrated high classification accuracy (100%) and a very high likelihood ratio for NLR (Exp(B) = 10.441), statistical significance was not reached. This could be explained by the small sample size and/or possible multicollinearity among other variables. The wide confidence interval of the likelihood ratio suggests that larger sample sizes are needed to draw definitive conclusions about the predictive value of NLR in FTD.

NLR results in FTD patients were positively correlated with BUN, glucose, AST, and ALT levels, which may indicate a broader systemic metabolic derangement in the pathogenesis of FTD. Furthermore, hemoglobin levels showed a consistent positive correlation with cognitive tests, suggesting potential links between oxygen-carrying capacity and cognitive performance. These results are clearly consistent with previous published studies suggesting that systemic comorbidities such as insulin resistance, hepatic damage, and anemia may influence the neurodegenerative process [6,13,20].

In contrast to studies suggesting that peripheral leukocyte counts have limited value in distinguishing between types of dementia [17], our study demonstrated significant group differences in neutrophil, lymphocyte, and NLR values. Furthermore, PCA identified NLR as the most effective parameter contributing to group separation, further demonstrating its discriminatory potential in multivariate models.

In our study, the association between NLR and FTD was evaluated, but some differences were found compared to population-based data in the literature. A retrospective cohort study in Hong Kong reported that high NLR levels were associated with a significantly increased risk of Alzheimer's disease and related dementias, but no similar correlation was found in non-Alzheimer's dementia (HR: 1.33; 95% CI: 0.60-2.95) [18]. However, our findings suggest that NLR may differ significantly in FTD, a non-Alzheimer type of dementia. This suggests that systemic inflammatory responses may play a role in the pathophysiology of FTD. Therefore, our results complement the findings of this large population study that the association between NLR and non-Alzheimer's dementia is not strong and are consistent with the prognostic value of inflammatory markers in FTD.

In a study conducted by Katipoğlu et al. on elderly patients who developed delirium in addition to dementia, NLR was shown to be an independent predictor of both short-term and long-term mortality (1 month and 1 year, respectively) [24]. This finding suggests that the inflammatory response may play a role in the prognosis of acute clinical manifestations, beyond the pathophysiology of dementia. Our findings are consistent with Katipoğlu et al.'s conclusion that "NLR is associated with mortality," suggesting that it may contribute to disease progression. Furthermore, considering the cutoff values determined in this study (3.86 for 1-year mortality and 5.25 for 1-month mortality), the distribution of NLR in our study fell both below and above these limits. This suggests that inflammation in FTD progresses with chronic, low-level, and ongoing activation.

A study conducted on patients with Alzheimer's disease demonstrated that the NLR is positively correlated with the severity of cognitive impairment, and higher NLR values are associated with lower MMSE scores [25]. In summary, it was found to be associated not only with the presence of dementia but also with the clinical severity. In our study, however, an increase in NLR did not show a clear dependence on the clinical stage, as seen in Alzheimer's disease. This finding may indicate that systemic inflammation plays a clearer and more adverse prognostic role in Alzheimer's disease, whereas inflammatory mechanisms play a more complex role in FTD. Therefore, while NLR may play a role in both the diagnostic and clinical severity of Alzheimer's disease, our study suggests that NLR is a parameter that reflects the presence of the disease in FTD, but its clinical correlation is limited.

Furthermore, our study has several limitations. First, the retrospective and single-center design may hinder the generalizability of the findings. Second, the cross-sectional nature of the study precludes causal inference. Third, although NLR is an accessible and inexpensive marker, it can be affected by numerous conditions, such as infection, medication use, and comorbid systemic diseases. Although we excluded individuals with significant chronic diseases, it is clear that many other contributing factors cannot be completely ignored. Finally, the relatively small sample size may have limited the power of the regression models to detect significant predictors. Future studies with larger cohorts and integration of radiologic findings, cerebrospinal fluid markers, and genomic data may better elucidate the clinical significance of NLR in the diagnosis, prognosis, or follow-up of FTD.

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Conclusion

Our study demonstrates that the neutrophil-to-lymphocyte ratio (NLR) is significantly elevated in patients with frontotemporal dementia, independent of other demographic and biochemical parameters. Our results support the potential role of systemic inflammation in the pathophysiology of FTD and highlight the NLR as a current, noninvasive, and cost-effective biomarker.

Our findings have several implications for clinical practice. First, the easy availability of NLR from a blood count suggests that it may be an inexpensive and accessible adjunctive parameter for the early diagnosis of important diseases such as FTD. Combined with clinical and radiological findings, an elevated NLR can be used as a useful marker, particularly in at-risk cases. Furthermore, the correlation of NLR with numerous biochemical parameters suggests that this ratio may reflect metabolic and other hematological pathologies, in addition to inflammatory processes. Considering all these factors, the NLR can be considered a practical tool for risk stratification and clinical follow-up of patients diagnosed with FTD. However, NLR alone has limited diagnostic value; its utility in clinical decision-making is much greater when used in conjunction with more comprehensive biomarker algorithms and advanced radiologic methods.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
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Ethical Approval
The study protocol was approved by the Etlik City Hospital Ethics Committee (date: 09.04.2025; acceptance Number: 2025-0288).

References

1. World Health Organization. Dementia Fact Sheet. https://www.who.int/news-room/fact-sheets/detail/dementia access date 06.08.2025.
2. Clinical and neuropathological criteria for frontotemporal dementia. The Lund and Manchester Groups. J Neurol Neurosurg Psychiatry. 1994;57:416-8.
3. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456-77.
4. Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology. 2011;76:1006-4.
5. Brun A. Frontal lobe degeneration of non-Alzheimer type. I. Neuropathology. Arch Gerontol Geriatr. 1987;6:193-208.
6. Kril JJ, Halliday GM. Pathological staging of frontotemporal lobar degeneration. J Mol Neurosci. 2011;45:379-83.
7. Onyike CU, Diehl-Schmid J. The epidemiology of frontotemporal dementia. Int Rev Psychiatry. 2013;25:130-7.
8. Fani L, Georgakis MK, Ikram MA, et al. Circulating biomarkers of immunity and inflammation, risk of Alzheimer's disease, and hippocampal volume: a Mendelian randomization study. Transl Psychiatry. 2021;11:291.
9. Ozturk A, Kara M. Diagnostic and prognostic significance of the lymphocyte/c-reactive protein ratio, neutrophil/lymphocyte ratio, and d-dimer values in patients with COVID-19. Biocell. 2022;46:2625-35.
10. Aktas G, Duman TT, Atak BM, et al. Irritable bowel syndrome is associated with novel inflammatory markers derived from hemogram parameters. Fam Med Prim Care Rev. 2020;2:107-10.
11. Duman TT, Aktas G, Atak BM, et al. Neutrophil to lymphocyte ratio as an indicative of diabetic control level in type 2 diabetes mellitus. Afr Health Sci. 2019;19:1602-6.
12. Bilgin S, Aktas G, Kocak MZ, et al. Association between novel inflammatory markers derived from hemogram indices and metabolic parameters in type 2 diabetic men. Aging Male. 2020;23:923-7.
13. Hosseini S, Shafiabadi N, Khanzadeh M, et al. Neutrophil to lymphocyte ratio in parkinson's disease: a systematic review and meta-analysis. BMC Neurol. 2023;23:333.
14. Sit M, Aktas G, Erkol H, et al. Neutrophil to lymphocyte ratio is useful in differentiation of malign and benign thyroid nodules. P R Health Sci J. 2019;38:60-3.
15. Bang J, Spina S, Miller BL. Frontotemporal dementia. Lancet. 2015;386:1672-82.
16. McCauley ME, Baloh RH. Inflammation in ALS/FTD pathogenesis. Acta Neuropathol. 2019;137:715-30.
17. Schröder S, Heck J, Groh A, et al. White blood cell and platelet counts are not suitable as biomarkers in the differential diagnostics of dementia. Brain Sci. 2022;12:1424.
18. Chou OHI, Zhou J, Li L, et al. The association between neutrophil-lymphocyte ratio and variability with new-onset dementia: a population-based cohort study. J Alzheimers Dis. 2023;94:547-57.
19. Ramos-Cejudo J, Johnson AD, Beiser A, et al. The neutrophil to lymphocyte ratio is associated with the risk of subsequent dementia in the Framingham Heart Study. Front Aging Neurosci. 2021;13:773984.
20. Lucero J, Gurnani A, Weinberg J, Shih LC. Neutrophil-to-lymphocyte ratio and longitudinal cognitive performance in Parkinson's disease. Ann Clin Transl Neurol. 2024;11:2301-13.
21. Mohammadi A, Mohammadi M, Almasi-Dooghaee M, Mirmosayyeb O. Neutrophil to lymphocyte ratio in Alzheimer's disease: a systematic review and meta-analysis. PLoS One. 2024;19:e0305322.
22. Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011;134:2456-77.
23. Sjögren M, Folkesson S, Blennow K, et al. Increased intrathecal inflammatory activity in frontotemporal dementia: pathophysiological implications. J Neurol Neurosurg Psychiatry. 2004;75:1107-11.
24. Katipoglu B, Naharci MI. Can the neutrophil-to-lymphocyte ratio predict mortality in community-dwelling older adults with delirium superimposed on dementia?. Aging Clin Exp Res. 2022;34:1819-26.
25. Chuang SY, Hsu YC, Chou KW, et al. Neutrophil-Lymphocyte ratio as a predictor of cerebral small vessel disease in a geriatric community: The I-Lan Longitudinal Aging Study. Brain Sci. 2023;13:1087.