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The Role of Maresin1 and Maresin2 Serum Levels in Prediction of Prognosis in Thrombectomised ischemic Stroke Patients

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Abstract

Objective: Although endovascular treatment (EVT) is widely accepted as the standard approach for acute ischemic stroke (IS), the prognostic determinants are not yet fully clarified. This study was designed to investigate the prognostic value of serum Maresin-1 (MaR1) and Maresin-2 (MaR2) levels in IS patients treated with EVT.

Method: In this prospective study at Dicle University Faculty of Medicine, Department of Neurology, Stroke Center, 59 IS patients undergoing EVT and 24 healthy controls were enrolled between March 1 and August 1, 2024. Serum levels of MaR1, MaR2, albumin, hemoglobin A1C, neutrophils, platelets, lipid profile, vitamin D, C-reactive protein, and ferritin were measured. Clinical data included baseline NIHSS, 3-month mRS, TICI recanalization, and pre-stroke comorbidities. Multivariable logistic regression analyses were performed to evaluate associations between MaR1, MaR2, stroke severity, and mortality.

Results: MaR1 and MaR2 concentrations were markedly reduced in the ischemic stroke group compared with healthy controls ($p = 0.04$ and $p = 0.02$). In parsimonious multivariable logistic regression analyses for 3-month mortality, neither MaR1 nor MaR2 showed an independent association, although both demonstrated borderline relationships after adjustment for age and baseline NIHSS. In contrast, stroke severity analysis revealed that higher MaR1 levels were independently associated with increased stroke severity (OR = 2.123; 95% CI, 1.18–3.25; $p = 0.047$), whereas MaR2 was not. Additionally, lower serum albumin levels emerged as an independent predictor of greater stroke severity in both models.

Conclusions: These findings suggest that MaR1 may reflect stroke severity rather than mortality, while albumin represents a key systemic determinant of disease severity. Maresins appear to act as inflammation-related biomarkers whose prognostic effects are modulated by overall metabolic and inflammatory status.

Key words: MaR1 and stroke; MaR2 and stroke; NIHSS and MaR1; Stroke Prognosis and maresin

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Trombektomi uygulanan iskemik inme hastalarında Maresin-1 ve Maresin-2 Serum düzeylerinin Prognozun öngörülmesindeki rolü

Öz

Amaç: Akut iskemik inmede (İS) endovasküler tedavi (EVT) standart yaklaşım olmakla birlikte, prognozu etkileyen faktörler hâlâ tam olarak aydınlatılamamıştır. Bu çalışma, EVT uygulanan İS hastalarında serum Maresin-1 (MaR1) ve Maresin-2 (MaR2) düzeylerinin prognostik önemini değerlendirmeyi amaçlamıştır.

Yöntemler: Bu prospektif çalışmada, Dicle Üniversitesi Tıp Fakültesi, Nöroloji Ana Bilim Dalı, İnme Merkezi'nde 1 Mart–1 Ağustos 2024 tarihleri arasında EVT uygulanan 59 İS hastası ve 24 sağlıklı kontrol değerlendirilmiştir. Serum MaR1, MaR2, albümin, hemoglobin A1c, nötrofil, trombosit, lipid profili, D vitamini, C-reaktif protein ve ferritin düzeyleri ölçülmüştür. Klinik veriler arasında başlangıç NIHSS skoru, 3. ay mRS değeri, TICI reküperasyon düzeyi ve inme öncesi komorbiditeler yer almıştır. MaR1, MaR2, inme ciddiyeti ve mortalite arasındaki ilişkileri incelemek için çok değişkenli lojistik regresyon analizleri yapılmıştır.

Bulgular: MaR1 ve MaR2 düzeyleri, iskemik inme grubunda sağlıklı kontrollere kıyasla anlamlı olarak daha düşüktü (sırasıyla p = 0,04 ve p = 0,02). Üç aylık mortalite için yapılan parsimoniyöz çok değişkenli lojistik regresyon analizlerinde, yaş ve başlangıç NIHSS skoru ile düzeltme sonrasında MaR1 ve MaR2'nin bağımsız bir ilişki göstermediği, ancak sınırda ilişkiler sergilediği izlendi. Buna karşılık, inme şiddeti analizinde yüksek MaR1 düzeylerinin daha ağır inme ile bağımsız olarak ilişkili olduğu saptandı (OR = 2,123; %95 GA: 1,18–3,25; p = 0,047), MaR2 için ise anlamlı bir ilişki gözlenmedi. Ayrıca düşük serum albümin düzeyleri, her iki modelde de artmış inme şiddetinin bağımsız bir belirleyicisi olarak bulundu.

Sonuç: Bu bulgular, MaR1'in mortaliteden ziyade inme şiddetini yansıtan bir biyobelirteç olabileceğini, albüminin ise hastalık şiddetinde önemli bir sistemik belirleyici olduğunu düşündürmektedir. Maresinlerin prognostik etkilerinin, genel metabolik ve inflamatuvar durum tarafından modüle edilen inflamasyon ilişkili biyobelirteçler olarak değerlendirilmesi gerektiği kanaatine varılmıştır.

Anahtar kelimeler: Mar1 ve inme, maR2 ve inme, NIHSS and MaR1, inme prognozu ve maresin.

INTRODUCTION

Globally, cerebrovascular diseases (CVD) rank as the second leading cause of death, just behind ischemic heart disease[1]. These diseases mostly present as ischemic strokes (87%), while parenchymal and subarachnoid hemorrhages account for 10% and 3% of cases, respectively[2]. Over the past ten years, major breakthroughs in acute ischemic stroke care have established endovascular mechanical thrombectomy (EVT) as a core therapeutic strategy. The main goal of this procedure is to salvage the ischemic penumbra in individuals who arrive within the appropriate treatment window. Even when EVT is performed promptly and successfully, a positive clinical recovery is not always ensured[3]. Consequently, researchers have been investigating specific biological mediators to better predict the prognosis of ischemic stroke patients treated with EVT. In this study, we aimed to investigate the significance of the newly identified mediators, Maresin1 (MaR1) and Maresin2 (MaR2), in relation to prognosis, recanalization, and complications in patients undergoing EVT.

Pioneering research on the resolution phase of inflammation was introduced by Dr. Charles Serhan's team at Harvard Medical School. They discovered a novel class of endogenous molecules termed specialized pro-resolving lipid mediators (SPMs) or immunoresolvents, which govern the clearance of inflammation[4,5]. The SPM family encompasses groups including protectins, lipoxins, and maresins, with maresins being derived from docosahexaenoic acid (DHA). MaR1 is endogenously synthesized from DHA by human macrophages[6]. Evidence suggests that MaR1 plays a significant role in the treatment of postoperative neuroinflammation and neurocognitive dysfunction, while also accelerating surgical

healing. Furthermore, it is a molecule that facilitates organ regeneration and tissue healing. Plasma concentrations of MaR1 have been shown to influence diabetes, obesity, and glucose and lipid metabolism. Collectively, these properties suggest that MaR1 may affect prognosis following ischemic stroke, highlighting the potential utility of this research[7,10]. Studies have demonstrated that MaR1 exhibits anti-inflammatory effects and reduces neuropathic pain[5]. The involvement of MaR1 has recently been examined across diverse neurological disorders, notably multiple sclerosis, Alzheimer's disease, ischemic stroke, and neuralgic pain[11-14]. Like MaR1, MaR2 is a DHA-derived mediator that possesses anti-inflammatory properties. MaR2 plays a significant role in pain pathways and has been studied in neurological disorders such as trigeminal neuralgia[15]. A study has demonstrated that MaR2 reduces apoptosis and inflammation in the heart of patients experiencing myocardial infarction while improving autophagy[16]. A literature review revealed no prior investigations regarding MaR2 in the context of stroke; therefore, our research serves as the first investigation to address this specific area.

METHODS

This research project was approved by the Ethics Dicle University Faculty of Medicine, Department of Neurology, Stroke Center under decision number 209/2024. Patients were selected from individuals who presented to the Dicle University Faculty of Medicine, Department of Neurology, Stroke Center between March 1, 2024, and July 1, 2024. The study population included 59 patients diagnosed with acute ischemic stroke who underwent endovascular treatment (EVT), along with 24 healthy volunteers who comprised the control group. Control participants were selected from healthy individuals who presented to our hospital for routine health check-ups.

Written informed consent was obtained from all patients who underwent endovascular thrombectomy (EVT) or, when applicable, from their first-degree relatives. Written informed consent was also obtained from all individuals in the healthy control group after providing detailed information about the study. Only individuals aged 18 years and older were included in the study. Exclusion criteria were defined as age under 18 years, refusal to provide informed consent, presence of known malignancy or rheumatological disease, a known diagnosis of a demyelinating disease, presence of active infection, or elevated infection-related parameters in blood tests. These exclusion criteria were applied equally to both the patient and control groups.

Blood samples were obtained immediately before the endovascular thrombectomy (EVT) procedure, at the time of femoral artery puncture. Collected data included demographic information such as age and sex; preoperative blood test results including albumin, hemoglobin A1c, neutrophil count, platelet count, total cholesterol, triglycerides, LDL, C-reactive protein, vitamin D, and ferritin levels; as well as medical history including atrial fibrillation, heart failure, coronary artery disease, hypertension, and diabetes mellitus. Additional clinical variables included the success of thrombolysis in cerebral infarction (TICI), National Institutes of Health Stroke Scale (NIHSS) scores at admission, modified Rankin Scale (mRS) scores at the 3-month follow-up, mortality rates, and procedure-related complications.

TICI is a grading system used to assess the degree of vascular recanalization achieved during the EVT procedure. In our study, a TICI score of 2b or higher was considered indicative of successful recanalization. The mRS is a functional outcome scale ranging from 0 to 6,

with a score of 6 indicating death. In this study, MaR1 and MaR2 levels were compared between patients who had an mRS score of 6 at 3 months and those in other outcome groups. The NIHSS, which was also recorded at admission, is used to evaluate the clinical status of patients with ischemic stroke, where higher scores reflect more severe neurological deficits. Patients were classified into mild, moderate, and severe stroke groups according to the NIHSS score. An NIHSS score of 0–8 was defined as mild stroke, 9–16 as moderate stroke, and scores greater than 16 as severe stroke.

Statistical Analysis

Data evaluations were conducted utilizing the SPSS statistical package, version 26.0 (SPSS Inc., Chicago, IL, USA). Based on the distribution profile of the variables, descriptive statistics were presented as mean ± standard deviation (SD), median alongside interquartile range (IQR), or as frequencies and percentages. Categorical data were compared using the chi-square (χ^2) test. For quantitative variables, the independent samples t-test was utilized if the data followed a normal distribution; otherwise, the Mann–Whitney U test was applied for skewed data. In scenarios where three or more groups were compared, a one-way ANOVA was utilized. The relationships between MaR1/MaR2 concentrations and clinical parameters (such as NIHSS and mRS) were analyzed via Spearman's rank correlation. To identify independent predictors associated with adverse outcomes at 3 months, a multivariable logistic regression model utilizing a forward selection method was generated. Variables demonstrating a p-value <0.10 in univariate models were included in the final regression analysis.

To assess the predictive capability of MaR1/MaR2 levels regarding mortality or stroke severity, a receiver operating characteristic (ROC) curve analysis was initially executed. Optimum threshold values for MaR1 and MaR2 were identified, allowing for the computation of sensitivity, specificity, and the Youden index. Based on these ROC-derived cutoff points, biomarker levels were stratified into "low" and "high" categories. Subsequently, the multivariable logistic regression analysis was repeated using these categorical variables. Before running this regression, multicollinearity was checked via the Variance Inflation Factor (VIF). A VIF exceeding 5 was accepted as a sign of collinearity. A p-value of <0.05 was regarded as statistically significant. An a priori power analysis (two-sided, α=0.05) indicated that the sample of 59 EVT-treated patients and 24 healthy controls provides 81% power to detect effects of Cohen's d ≈0.70 or larger. While the reduced number of participants in the control group is a limiting factor, it was factored into the power analysis and will be managed via appropriate statistical techniques.

Biochemical Measurements

Following an overnight fast of 12 hours, blood samples were drawn from all study participants. These specimens were collected into standard biochemistry tubes and centrifuged for 15 minutes at 1500 g. Routine laboratory tests were performed immediately following centrifugation. For the determination of Maresin-1 (MaR1) and Maresin-2 (MaR2) levels, 10 cc of blood was drawn into standard clinical chemistry test tubes and centrifuged at 1500 g for 20 minutes to obtain serum. The obtained serum samples were kept frozen at −80°C until the day of analysis. Prior to testing, all samples were brought to room temperature. The concentrations of serum MaR1 and MaR2 were determined via commercial enzyme-linked immunosorbent assay (ELISA) kits tailored for Human MaR1 and MaR2 (Sunred Biological Technology, Shanghai, China). Every sample was tested in duplicate, with the average values utilized for statistical assessments. Intra-assay and inter-assay coefficients of variation were <10% and <12%, respectively, in accordance with the manufacturer's specifications. All ELISA

procedures were carried out strictly following the protocols provided by the manufacturer, utilizing a BioTek ELx50 Microplate Washer alongside a BioTek ELx800 Microplate Reader (BioTek Instruments, Inc., USA).

RESULTS

The study included 83 individuals, comprising 24 healthy controls and 59 patients with ischemic stroke who underwent EVT. The mean age of the stroke group was significantly higher than that of the control group (p = 0.02). The average age was 64.5 ± 15.8 years in the stroke group and 53.6 ± 11.1 years in the control group. Sex distribution did not differ significantly between the two groups (p = 0.062), as the proportion of males and females was similar. Both MaR1 and MaR2 concentrations were found to be significantly reduced in patients compared with controls (p = 0.04 and p = 0.02, respectively). Albumin and total cholesterol concentrations were markedly reduced in the patient cohort (p = 0.001 and p = 0.02). In contrast, CRP, vitamin D, and ferritin values were substantially elevated among patients (p = 0.02, p = 0.01, and p = 0.02, respectively). There were no meaningful differences between the groups with respect to HbA1c, neutrophil counts, platelet counts, triglyceride levels, or LDL measurements. In the EVT-treated patient group, the TICI success rate was 89.8%. The complication rate was 13.6%, and the mortality rate was 22% in this group (Table 1).

Table I: Demographic, clinical, and laboratory characteristics of the patient and control groups

	Control (n:24)	Disease (n:59)	*p*
Age (SD)	53.6±11.1	64.5±15.8	**0,02***
Gender (%)			
Male	15 (62,5%)	23 (39%)	0,062
Female	9 (37,5%)	36 (61%)	
MaR1(mean±SD)	1757,84±3058	938,6±1925,61	**0,04***
MaR2(mean±SD)	4,35±2,71	2,97±1,97	**0,02***
Laboratuar (mean±SD)			
Albumine	42,24±4,68	35,58±6,05	**0,001***
HbA1c	5,21±0,5	6,26±1,41	0,584
Neutrophil	4,58±2,24	9,03±4,24	0,673
Platelet	268,21±81,92	267,32±79,66	0,963
Total colesterol	172,73±30,61	193,74±49,52	**0,02***
Trigiliserit	141,13±84,57	129,41±58,1	0,790
LDL	106,67±24,91	122,98±32,16	0,592
CRP	2,54±2,14	48,04±27,35	**0,02***
D vitamine	20,61±6,65	13,82±12,76	**0,01***
Ferritine	58,21±56,91	115,11±81,75	**0,02***
Clinical Characteristics			
Hypertension	---	39 (66.1%)	---
Diabetes	---	24 (40.7%)	---
Coronary Artery Disease	---	27 (45.8%)	---
Atrial Fibrillation	---	19 (32.2%)	---
Heart Failure	---	11 (18.6%)	---
TICI succesfull n(%)	---	53 (89.8%)	---
Admission NIHSS			
Minör stroke (0-8)	---	2 (3.4%)	---
Moderate stroke (9-16)	---	13 (22.1%)	---
Severe stroke (>16)	---	44 (74.5%)	---
mRS (0-3;ındependent)	---	35 (59.3 %)	---
mRS (4-6;dependent) ---		24 (40,7%)	---
Complicatıon n(%)	---	8 (13.6%)	---
Mortality n(%)	---	13 (22%)	---

MaR1: Maresin 1;MaR2: Maresin 2;CRP: C reaktive Protein; mRS: modified Rankin Scale; TICI: Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale ; SD: Standart Deviation;p value:Mann Whitney U, t-test and Chi-Square test

Figure 1 illustrates the distribution of MaR1 levels between the patient group and healthy controls. Figure 2 presents a comparative assessment of MaR2 levels between patients and healthy individuals.

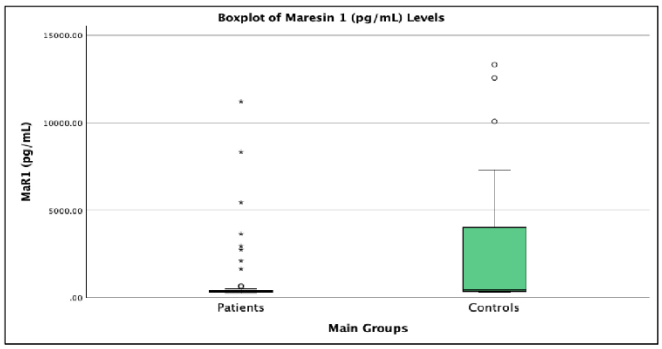

Figure 1. Box plot showing the comparison of Maresin 1 levels between the patient and control groups

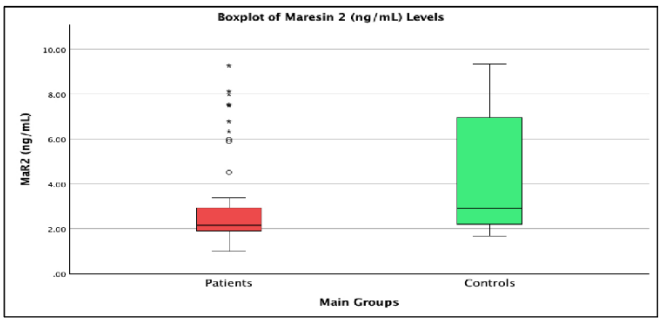

Figure 2. Box plot showing the comparison of Maresin 2 levels between the patient and control groups

In Table 2, differences in MaR1 and MaR2 levels across non–normally distributed clinical and patient-related variables were assessed using the Mann–Whitney U test, while comparisons among the three NIHSS-based stroke severity subgroups (minor, moderate, and severe) were performed with the Kruskal–Wallis test. MaR2 levels were significantly higher in survivors compared to non-survivors (p = 0.014), whereas although MaR1 levels were also higher in survivors, this difference did not reach statistical significance (p = 0.129). Patients with hypertension exhibited significantly elevated MaR1 levels relative to those without hypertension (p = 0.044). In contrast, the presence of diabetes mellitus, coronary artery disease, atrial fibrillation, or heart failure had no significant effect on MaR1 or MaR2 levels (all p > 0.05). No significant differences in MaR1 or MaR2 concentrations were observed among the minor, moderate, and severe stroke subgroups (p = 0.133 and p = 0.333, respectively), so no post-hoc analyses were conducted. Finally, Spearman correlation analyses between MaR1/MaR2 levels and continuous variables (age and laboratory parameters) revealed no statistically significant associations (all p > 0.05).

Table II: Comparison of MaR1 and MaR2 levels according to clinical features in patients with ischemic stroke treated with EVT

	MaR1	*p*	MaR2	*p*
Gender – median(IQR)				
Female	343,18(180,82)	0,924	2,25(1,96)	0,721
Male	349,71(239,42)		2,35(2,03)	
TICI-median(IQR)				
Succesfull	333,37(131,37)	0,726	2,13(1,12)	0,347
Unsuccesfull	344,49(42,23)		2,41(0,89)	
Complication-median(IQR)				
None	341,77(127,66)	0,207	2,17(1,15)	0,195
Yes	315,82(35,72)		1,88(1,23)	
mRS-median(IQR)				
Independent (0-3)	339,28(161,81)	0,655	2,17(0,96)	0,926
Dependent (4-6)	336,88(116,51)		2,24(1,19)	
Admission NIHSS	395,21(95,27)	0,333	2,11(0,98)	0,133
Mortality-median(IQR)				
Survıval	417,9(121,31)		2,96(1,78)	
Death	331,52(71,99)	0,129	2,02(0,79)	**0,014***
Clinical Characteristics-median(IQR)				
Hypertension				
None	323,79(60,57)		1,99(1,06)	
Yes	349,71(124,12)	**0,044***	2,31(1,31)	0,087
Diabetes				
None	329,78(95,52)		2,13(0,83)	
Yes	357,17(104,32)	0,167	2,33(0,92)	0,119
Coronary Artery Disease				
None	331,52(91,15)		2,24(1,10)	
Yes	344,48(107,52)	0,951	2,02(1,05)	0,390
Atrial Fibrillation				
None	336,32(156,18)		2,17(1,26)	
Yes	338,91(68,17)	0,994	2,17(0,72)	0,858
Heart Failure				
None	327,84(90,09)		2,15(0,79)	
Yes	417,9(127,18)	0,052	2,85(1,29)	0,289

MaR1: Maresin 1;MaR2: Maresin 2; ; mRS: modified Rankin Scale; TICI: Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; IQR: Interquartile Range: p value: Mann Whitney U

The predictive capacity of MaR1 was limited, as indicated by an AUC value of 0.639. A cutoff level of 413.65 pg/mL provided a sensitivity of 53.8% and a specificity of 80.4%, with a Youden index of 0.343. In contrast, MaR2 exhibited superior discriminative ability, with an AUC of 0.724. At a cutoff of 2.88 ng/mL, MaR2 achieved a sensitivity of 61.5% and specificity of 82.6% (Youden index: 0.441). These results suggest that MaR2 outperforms MaR1 in predicting mortality (Figure 3).

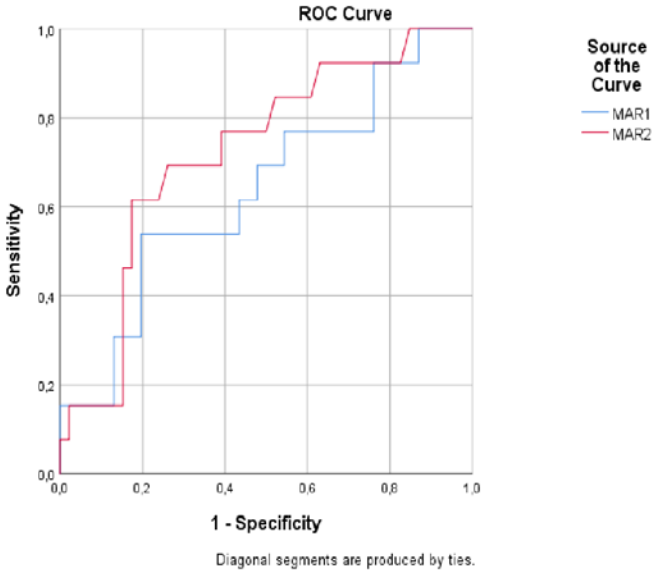

Figure 3: ROC curve analysis of MaR1 and MaR2 for predicting mortality in ischemic stroke patients treated with EVT

Multivariable logistic regression analyses assessing the association of MaR1 and MaR2 levels with 3-month mortality in EVT-treated ischemic stroke patients are summarized in Table 3. A significant degree of multicollinearity was detected between MaR1 and MaR2 (VIF = 6.2); therefore, each biomarker was entered into separate regression models.

Table 3 presents the parsimonious multivariable logistic regression analyses evaluating factors associated with 3-month mortality in EVT-treated ischemic stroke patients. After adjustment for age and baseline NIHSS, neither MaR1 nor MaR2 showed an independent association with mortality (MaR1: OR = 1.51, 95% CI 0.82–1.70, p = 0.073; MaR2: OR = 1.34, 95% CI 0.95–1.90, p = 0.095). Baseline NIHSS demonstrated a borderline association with mortality (OR = 1.14, 95% CI 0.99–1.21, p = 0.068), while age also showed a near-significant relationship (OR = 1.05, 95% CI 0.91–1.15, p = 0.066). These findings indicate that post-EVT mortality is primarily influenced by baseline neurological severity rather than individual inflammatory biomarkers.

Table III: Parsimonious multivariable logistic regression analysis of factors associated with 3-month mortality in EVT-treated ischemic stroke patients

	p	OR	%95 CI (lower-upper)		*p*	OR	%95 CI(lower-upper)
MaR1	0,073	1,512	0,824-1,702	**MaR2**	0,095	1,344	0,950-1,902
Age	0,066	1,052	0,912-1,151	**Age**	0,053	1,056	0,999-1,116
NIHSS	0,068	1,144	0,990-1,214	**NIHSS**	0,080	1,136	0,985-1,310

MaR1: Maresin 1;MaR2: Maresin 2; NIHSS: National Institutes of Health Stroke Scale; The models were limited to three variables (age, baseline NIHSS score, and MaR1 or MaR2) to ensure adequate events-per-variable ratios.

Table 4 summarizes the parsimonious multivariable logistic regression models assessing factors associated with stroke severity. In the MaR1 model, higher MaR1 levels were independently associated with greater stroke severity (OR = 2.12, 95% CI 1.18–3.25, p = 0.047). In contrast, MaR2 did not demonstrate a significant independent association with stroke severity (OR = 0.82, 95% CI 0.61–1.10, p = 0.178). Importantly, lower serum albumin levels emerged as a consistent independent predictor of increased stroke severity in both models (MaR1 model: OR = 0.85, 95% CI 0.74–0.99, p = 0.039; MaR2 model: OR = 0.85, 95% CI 0.73–0.99, p = 0.038), whereas age was not

independently associated with stroke severity (MaR1 model: OR = 0.99, 95% CI 0.95–1.04, p = 0.735; MaR2 model: OR = 0.99, 95% CI 0.95–1.04, p = 0.732).

Table IV: Parsimonious multivariable logistic regression analysis of factors associated with stroke severity in EVT-treated ischemic stroke patients

	p	OR	%95 CI (lower-upper)		*p*	OR	%95 CI(lower-upper)
MaR1	**0,047***	2,123	1,18-3,25	**MaR2**	0,178	0,817	0,609-1,096
Albumin	**0,039***	0,854	0,735-0,992	**Albumin**	**0,038***	0,852	0,733-0,991
Age	0,735	0,993	0,951-1,036	**Age**	0,732	0,992	0,951-1,035

MaR1: Maresin 1;MaR2: Maresin 2; Stroke severity was defined according to NIHSS-based classification. To ensure adequate events-per-variable ratios and avoid model overfitting, the multivariable models were restricted to three variables (age, serum albumin level, and MaR1 or MaR2), with MaR1 and MaR2 entered into separate models.

DISCUSSION AND CONCLUSIONS

EVT is now firmly established as the primary treatment approach for acute ischemic stroke. In our cohort, the rate of functional independence at 3 months (mRS 0–3) was 50.8%, corresponding to a functional dependence rate (mRS 4–6) of 49.2%. These outcomes are consistent with reported results for anterior-circulation EVT cases. Despite a high successful recanalization rate (TICI ≥2b) of 89.2%, approximately half of the patients experienced poor functional outcome, indicating that factors beyond mechanical reperfusion influence post-EVT prognosis.

Three principal pathophysiological mechanisms contribute to neuronal injury after acute ischemia: ischemic necrosis resulting from oxygen deprivation in the territory of the occluded vessel[17]; increased generation of reactive oxygen species (ROS) during reperfusion, which exacerbates cellular damage [18,19]; and inflammation triggered by ischemia, with cytokine/chemokine release that propagates neuronal injury[20]. Our study specifically targeted this inflammatory component of post-ischemic injury.

MaR1 and MaR2 are lipid mediators derived from DHA and belong to the specialized pro-resolving mediator (SPMs) family. These mediators have been increasingly recognized for their anti-inflammatory and tissue-repair promoting properties; maresins are omega-3–derived lipids that actively promote resolution of inflammation[21]. Experimental studies of MaR1 have demonstrated attenuation of cerebral ischemia–reperfusion injury. For example, in rodent models of cerebral ischemia/reperfusion, MaR1 administration reduced inflammatory responses and mitochondrial injury, decreased infarct volume and neurological deficits, and inhibited nuclear translocation of NF-κB p65. Xian et al. showed that MaR1 activates the SIRT1 pathway, reducing caspase-3 activity and NF-κB signaling, thereby preventing neuronal apoptosis[22]. Recent work also indicates that MaR1 suppresses inflammasome-related caspase-3/GSDME pyroptosis and reduces pro-inflammatory cytokines such as TNF-α IL-1β and IL-6[23]. Collectively, these preclinical data support a potent anti-inflammatory and neuroprotective role for MaR1.

Human data are consistent with the preclinical evidence: MaR1 has been shown to exert inflammation-modulating and protective effects in models relevant to neurodegeneration. Tan et al. reported that MaR1 treatment of human monocyte-derived microglia inhibited pro-inflammatory cytokine production and enhanced Aβ42 phagocytosis, supporting a role in Alzheimer's disease models[24]. Clinical observations have likewise reported reduced plasma MaR1 levels in patients with

subarachnoid hemorrhage, cerebral infarction, and intracerebral hemorrhage relative to healthy controls[25], a finding that parallels our observation of significantly lower MaR1 levels in ischemic stroke patients compared with controls ($p = 0.004$). In the present study, multivariable analyses demonstrated that MaR1 was independently associated with stroke severity but not with 3-month mortality. This finding suggests that MaR1 may primarily reflect the intensity of neuroinflammatory activation and tissue injury at presentation rather than serving as a direct determinant of survival, which is influenced by multiple systemic and clinical factors. Interestingly, MaR1 levels were higher in patients with a history of hypertension. This seemingly paradoxical finding may reflect a compensatory upregulation of endogenous resolution pathways in response to chronic low-grade inflammation associated with hypertension. Chronic inflammatory states have been shown to induce increased biosynthesis of specialized pro-resolving mediators as an adaptive response; however, this response may be quantitatively insufficient during acute ischemic insults[5,6]. Accordingly, despite relatively higher MaR1 levels in hypertensive patients, insufficient resolution capacity may still contribute to severe neurological injury and increased mortality following acute ischemic stroke. The findings related to vitamin D levels were unexpected. Although vitamin D has recognized immunomodulatory and neuroprotective effects, acute-phase vitamin D measurements may be confounded by systemic inflammation, stress response, nutritional status, and seasonal variability. Moreover, vitamin D levels obtained during the acute stroke phase may not accurately reflect baseline vitamin D status. Therefore, the lack of a clear association between vitamin D levels and clinical outcomes in our cohort should be interpreted with caution and warrants further investigation in longitudinal studies[26]. Overall, our results support the hypothesis that MaR1 functions as a protective mediator in neuroinflammatory processes following cerebral ischemia[22-25].

An additional important finding of this study is the independent association between low serum albumin levels and increased stroke severity. Albumin is a well-established marker of systemic inflammation, nutritional status, and physiological reserve, and hypoalbuminemia has been consistently linked to worse neurological deficits and unfavorable outcomes in acute ischemic stroke. Reduced albumin levels may exacerbate oxidative stress, endothelial dysfunction, and cerebral edema, thereby contributing to greater initial stroke severity[27].

MaR2, a DHA-derived maresin structurally related to MaR1, has been far less investigated. Existing studies are primarily preclinical and address diverse inflammatory conditions. For example, Yu et al. demonstrated that MaR2 reduced airway inflammation, inflammasome activation and oxidative stress (reduced MDA, increased SOD and GSH) in an experimental asthma model, with significant reductions in histologic inflammation and BALF cytokines[25]. MaR2 has also been reported to attenuate mechanoreceptive hyperalgesia in neuropathic pain models and to suppress inflammatory responses[21,28]. However, to date there is essentially no clinical literature evaluating MaR2 in cerebrovascular disease. In our study, although MaR2 levels were significantly reduced in ischemic stroke patients, MaR2 did not show an independent association with stroke severity or mortality after multivariable adjustment, suggesting a more limited or context-dependent clinical role.

Taken together, the observed reductions in both MaR1 and MaR2 in ischemic stroke patients, and their associations with poorer clinical outcomes, are congruent with the concept that insufficient activation of endogenous resolution

pathways contributes to adverse post-ischemic evolution. Our findings indicate that MaR1 is primarily linked to stroke severity, while albumin represents a robust systemic determinant of neurological burden, underscoring the interplay between inflammation resolution and overall physiological reserve in EVT-treated ischemic stroke patients.

LIMITATIONS

The first and most important limitation of the study is the small sample size in both the patient and control groups. The second limitation is that the medications used by the patients were not classified; these medications may influence maresin levels. Third, although a healthy control group was included, it remains unclear whether maresin levels develop secondarily as a consequence of neuronal injury, since pre-stroke maresin levels in the patients are unknown. In addition, the presence of a statistically significant age difference between the patient and control groups should be considered a potential confounding factor in the interpretation of the results. In addition, the presence of a statistically significant age difference between the patient and control groups should be considered a potential confounding factor; however, age was adjusted for in all multivariable analyses.

Ethics Committee Approval: This research project was approved by the Ethics . Patients were selected from individuals who presented to the Dicle University Faculty of Medicine, Department of Neurology, Stroke Center between March 1, 2024, and July 1, 2024 under decision number 209/2024. Patients were selected from individuals who presented to the Dicle University Faculty of Medicine, Department of Neurology, Stroke Center between March 1, 2024, and July 1, 2024.

Conflict of Interest: The author(s) declare that there is no financial conflict of interest related to this article.

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REFERENCES

1. Alexandru R, Terecoasă EO, Băjenaru OA, Tiu C. Etiologic classification of ischemic stroke: Where do we stand? Clin Neurol Neurosurg. 2017;155:1-9.

2. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2016 update: A report from the American Heart Association. Circulation. 2016;133:e38-360.

3. Şengeze N, Giray S. The relationship between mean platelet volume, platelet count, platelet lymphocyte ratio, and recanalization success in first-pass thrombectomy of middle cerebral artery occlusions. Turk J Neurol. 2020;26:133-7.

4. Serhan CN. Resolution phase of inflammation: Novel endogenous anti-inflammatory and pro-resolving lipid mediators and pathways. Annu Rev Immunol. 2007;25:101-37.

5. Serhan CN, Chiang N, Dalli J, Levy BD. Lipid mediators in the resolution of inflammation. Cold Spring Harb Perspect Biol. 2014;7:a016311.

6. Serhan CN, Petasis NA. Resolvins and protectins in inflammation-resolution. Chem Rev. 2011;111:5922-43.

7. Serhan CN, Dalli J, Karamnov S, et al. Macrophage proresolving mediator maresin 1 stimulates tissue regeneration and controls pain. FASEB J. 2012;26:1755-65.

8. Wei J, Su W, Zhao Y, et al. Maresin 1 promotes nerve regeneration and alleviates neuropathic pain after nerve injury. J Neuroinflammation. 2022;19:32.

9. Miao T, Huang B, He N, et al. Decreased plasma maresin 1 concentration is associated with diabetic foot ulcer. Mediators Inflamm. 2020;2020:4539035.

10. Saito-Sasaki N, Sawada Y, Nakamura M. Maresin-1 and inflammatory disease. Int J Mol Sci. 2022;23:1367.

11. Wang Y, Leppert A, Tan S, et al. Maresin 1 attenuates pro-inflammatory activation induced by β-amyloid and stimulates its uptake. J Cell Mol Med. 2021;25:434-47.

12. Francos-Quijorna I, Santos-Nogueira E, Gronert K, et al. Maresin 1 promotes inflammatory resolution, neuroprotection, and functional neurological recovery after spinal cord injury. J Neurosci. 2017;37:11731-43.

13. Xian W, Li T, Li L, Hu L, Cao J. Maresin 1 attenuates the inflammatory response and mitochondrial damage in mice with cerebral ischemia/reperfusion in a SIRT1-dependent manner. Brain Res. 2019;1711:83-90.

14. Fattori V, Pinho-Ribeiro FA, Staurengo-Ferrari L, et al. The specialised pro-resolving lipid mediator maresin 1 reduces inflammatory pain with a long-lasting analgesic effect. Br J Pharmacol. 2019;176:1728-44.

15. Lopes RV, Baggio DF, Ferraz CR, et al. Maresin-2 inhibits inflammatory and neuropathic trigeminal pain and reduces neuronal activation in the trigeminal ganglion. Curr Res Neurobiol. 2023;4:100093.

16. Zhang J, Li C, Shuai W, et al. Maresin-2 fine-tunes ULK1 O-GlcNAcylation to improve post-myocardial infarction remodeling. Eur J Pharmacol. 2024;962:176223.

17. Chen YC, Ma NX, Pei ZF, et al. A NeuroD1 AAV-based gene therapy for functional brain repair after ischemic injury through in vivo astrocyte-to-neuron conversion. Mol Ther. 2020;28:217-34.

18. Hu X, Wu D, He X, et al. circGSK3β promotes metastasis in esophageal squamous cell carcinoma by augmenting β-catenin signaling. Mol Cancer. 2019;18:160.

19. Karaaslan F, Demir F, Yılmaz R, Akıl E. Total oxidant/antioxidant status, copper and zinc levels in acute ischemic stroke patients after mechanical thrombectomy. Clin Neurol Neurosurg. 2023;229:107718.

20. Ren X, Hu H, Farooqi I, Simpkins JW. Blood substitution therapy rescues the brain of mice from ischemic damage. Nat Commun. 2020;11:4078.

21. Zhao Y, Zhang X, Chen X, Wei Y. Neuronal injuries in cerebral infarction and ischemic stroke: From mechanisms to treatment. Int J Mol Med. 2022;49:15.

22. Qiu Y, Wu Y, Zhao H, Sun H, Gao S. Maresin 1 mitigates renal ischemia/reperfusion injury in mice via inhibition of the TLR4/MAPK/NF-κB pathways and activation of the Nrf2 pathway. Drug Des Devel Ther. 2019;13:739-45.

23. Yin P, Wang S, Wei Y, et al. Maresin 1 decreased microglial chemotaxis and ameliorated inflammation induced by amyloid-β42 in neuron-microglia co-culture models. J Alzheimers Dis. 2020;73:503-15.

24. Yu CX, Shi ZA, Ou GC, et al. Maresin-2 alleviates allergic airway inflammation in mice by inhibiting the activation of NLRP3 inflammasome, Th2 immune response and oxidative stress. Mol Immunol. 2022;146:78-86.

25. Albayrak S, Aydin MA, Ugur K, et al. Subfatin, asprosin, alamandine and maresin-1 in cerebral ischemia, intracranial and subarachnoid hemorrhages. Eur Rev Med Pharmacol Sci. 2023;27:4471-80.

26. Daubail B, Jacquin A, Guilland JC, et al. Serum 25-hydroxyvitamin D predicts severity and prognosis in stroke patients. Eur J Neurol. 2013;20:57-61.

27. Zhou H, Wang A, Meng X, et al. Low serum albumin levels predict poor outcome in patients with acute ischaemic stroke or transient ischaemic attack. Stroke Vasc Neurol. 2021;6:458-66.

28. Zhao M, Xian W, Liu W, et al. Maresin 1 alleviates neuroinflammation by inhibiting caspase-3/GSDME-mediated pyroptosis in a cerebral ischemia–reperfusion model. J Stroke Cerebrovasc Dis. 2024;33:107789.