

ORIGINAL ARTICLE

ÖZGÜN ARAŞTIRMA

**IN THE EARLY PERIOD OF ACUTE ISCHEMIC STROKE MORTALITY SCORES AND INFLAMMATORY
MARKERS CAN PREDICT THE NEED FOR INTUBATION**

Hasan Hüseyin KOZAK, Ahmet BUĞRUL, Fatih TOL

Necmettin Erbakan University Meram Medical Faculty, Department of Neurology, Konya, TÜRKİYE

ABSTRACT

INTRODUCTION: In this study, we aimed to evaluate the predictability of invasive mechanical ventilation requirement after stroke based on mortality scores and inflammatory parameters.

METHODS: The demographic and clinical characteristics of the patients admitted after acute ischemic stroke, as well as mortality scores and inflammatory parameters within the first 24 hours of hospitalization in the stroke intensive care unit were evaluated retrospectively.

RESULTS: 48 of 157 patients were included in the study, 13 were intubated and followed up with invasive mechanical ventilation, and 35 without being intubated. Glasgow Coma Score (GCS) of intubated and non-intubated cases were 7,9±3,5 and 13,6±2,4, respectively, National Institutes of Health Stroke Scale (NIHSS) 15,7±7,2 and 7,9±6, Simplified Acute Physiology Score II (SAPS II) 58,9±12 and 25,6±10,7, Acute Physiology and Chronic Health Evaluation II (APACHE II) 18,6±4,1 and 8,2±4,7, Sequential Organ Failure Assessment Score (SOFA) score was found to be 6,6±2 and 2,2±1,9, and a statistical significance was found between the two groups. Neutrophil / lymphocyte ratio (NLR) of the patients who were followed up with and without intubation was 6,1 (3,8-15,6) and 3,0 (1,8-4,5), platelet / lymphocyte ratio (PLR) 185 (157-245) and 120 (75-219) and C-reactive Protein (CRP) was 6,5 (4,6-58,0) and 3,7 (2,0-11,2), and a statistical significance was found between the two groups. Only SAPS II was found to be significant in multivariate analysis.

DISCUSSION AND CONCLUSION: In this study, it was determined that the mortality and morbidity prediction scores (APACHE II, SAPS II, SOFA) and inflammation parameters (CRP, NLR, PLR) can predict the need for invasive mechanical ventilation associated with stroke.

Keywords: Acute ischemic stroke, mortality score, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, mechanical ventilation.

Address for Correspondence: Ahmet Buğrul, MD. Necmettin Erbakan University Meram Medical Faculty, Department of Neurology, Konya, Türkiye.

Phone: +90 332 223 60 00

E-posta: ahmet.bugrul@gmail.com

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ORCID IDs: Hasan Hüseyin Kozak [0000-0001-6904-8545](https://orcid.org/0000-0001-6904-8545), Ahmet Buğrul [0000-0002-6208-2553](https://orcid.org/0000-0002-6208-2553), Fatih Tol [0000-0002-0274-4367](https://orcid.org/0000-0002-0274-4367).

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AKUT İSKEMİK İNMENİN ERKEN DÖNEMİNDE MORTALİTE SKORLARI VE İNFLAMATUAR BELİRTEÇLER MEKANİK VENTİLASYON İHTİYACINI ÖNGÖREBİLİR

ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada inme sonrası invaziv mekanik ventilasyon gereksiniminin mortalite skorları ve inflamatuvar parametrelere göre öngörülebilirliğini değerlendirmeyi amaçladık.

YÖNTEM ve GEREÇLER: Akut iskemik inme sonrası başvuran olguların demografik, klinik özellikleri ile birlikte inme yoğun bakımına yatırıldıkları ilk 24 saatin içinde mortalite skorları ve inflamatuvar parametreleri geriye dönük olarak değerlendirildi.

BULGULAR: 157 hastanın 48'i çalışmaya dahil edildi, 13'ü entübe edilerek invaziv mekanik ventilasyon ile takip edildi ve 35'i entübe edilmeden takip edildi. Entübe ve entübe olmayan olguların Glasgow Coma Score (GCS) sırasıyla 7,9±3,5 ve 13,6±2,4, National Institutes of Health Stroke Scale (NIHSS) 15,7±7,2 ve 7,09±6, Simplified Acute Physiology Score II (SAPS II) 58,9±12 ve 25,6±10,7, Acute Physiology and Chronic Health Evaluation II (APACHE II) 18,6±4.1 ve 8,2±4,7, Sequential Organ Failure Assessment Score (SOFA) 6,6±2 ve 2,2±1,9 olarak bulundu ve iki grup arasında istatistiksel olarak anlamlı bulundu. Entübasyonlu ve entübasyonsuz takip edilen hastaların medyan Nötrofil/lenfosit oranı (NLO) 6,1 (3,8-15,6) ve 3,0 (1,8-4,5), Platelet/lenfosit oranı (PLO) 185 (157-245) ve 120 (75-219) ve C-reactive Protein (CRP) 6,5 (4,6-58,0) ve 3,7 (2,0-11,2) idi ve iki grup arasında istatistiksel olarak anlamlılık bulundu. Yapılan çok değişkenli analizde sadece SAPS II anlamlı olarak bulundu.

TARTIŞMA ve SONUÇ: Bu çalışmada mortalite ve morbidite tahmin skorları (APACHE II, SAPS II, SOFA) ile inflamasyon parametrelerinin (CRP, NLO, PLO) inme ile ilişkili invaziv mekanik ventilasyon ihtiyacını öngörebileceği belirlendi.

Anahtar Sözcükler: Akut iskemik inme, mortalite skoru, nötrofil-lenfosit oranı, trombosit-lenfosit oranı, mekanik ventilasyon.

INTRODUCTION

Inflammatory processes are triggered by proinflammatory mediator spread to the environment after both the shear stress of the vessels due to decreased blood flow and the death of nerve cells (1). Post-stroke inflammatory response has both local and systemic detrimental effects. Its local effects are manifested by free oxygen radicals released from neutrophils, neuron and blood-brain barrier damage associated proteinase and matrix metalloproteinase. Respiratory failure, one of its systemic effects and the most important one, occurs due to immunosuppression due to decreased lymphocyte count and effects related to cytokine release (2,3). Respiratory failure is the most common extra-cerebral complication in neurology intensive care (4). Mechanical ventilator need of the patients with ischemic stroke varies between 5-8% (5). Glasgow Coma Score (GCS) <9, signs of increased intracranial pressure, generalized (tonic-clonic) seizures, infarct size >2/3 of the middle cerebral artery territory, and midline shift on imaging are predictors for intubation (6). The need for mechanical ventilators is an indicator of poor prognosis in stroke patients, with a mortality rate of 40-80% (7). The ratio of increasing neutrophil and platelet counts and decreasing lymphocyte

counts after inflammatory response has been used as an inflammatory marker as a poor prognosis predictor in stroke patients (8,9). In this study, we retrospectively evaluated the patients who were hospitalized in the intensive care unit (ICU) with acute ischemic stroke (AIS). Patients who were intubated or not intubated in terms of demographic characteristics, laboratory findings, inflammatory markers, radiological and clinical indicators were researched. We evaluated whether mortality scores and inflammatory parameters could predict the intubation requirements of these patients.

METHODS

In order to perform the study, ethical approval was obtained from Necmettin Erbakan University Ethical Committee (Number: 2020/2684, Date: 23rd October 2020). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. In this study, the patients who were hospitalized in the stroke ICU with the diagnosis of AIS between June 2019 and June 2020 followed up with intubation (intubated in the first 7 days) and without intubation were retrospectively analyzed. All

patients were followed up by the neurology intensive care team (one neurologist, and one intensive care specialist) in the tertiary stroke ICU. The patients under 18 years of age, who had hemorrhagic stroke, inadequate data, not admitted to hospital within the first 24 hours, history of cerebrovascular accident (CVA) in the last six months, modified Rankin Scale (mRS) score >2 before admission, with signs of active infection at admission, who received immunosuppressive treatment and were diagnosed with cancer were excluded from the study (Figure 1).

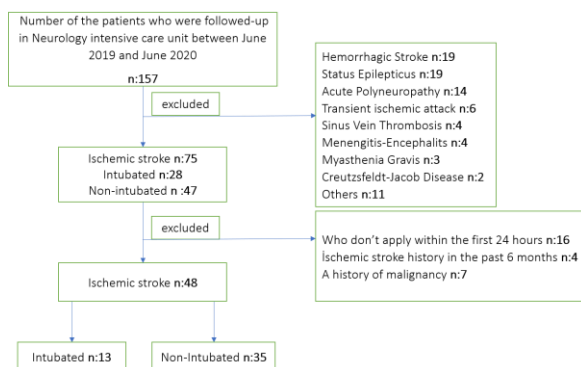


Figure 1. Study recruitment profile.

The cases were evaluated in a total of 69 different parameters, including categories such as gender, age, co-morbidities, state of consciousness, mortality prediction and scales of multi-organ failure, clinical and laboratory parameters associated with infection, and clinical conditions during hospitalization in the ICU. In addition, diffusion MRI and brain CT images taken within the first 24 hours were examined. Classification of infarct areas according to vascular supply was made with the aid of radiological images based on The Oxfordshire Community Stroke Project (OCSP). Trial of Org 10172 in Acute Stroke Treatment (TOAST) (10) was used for the classification of ischemic stroke etiology, Glasgow Coma Score (GCS) (11) for the measurement of consciousness levels, and National Institutes of Health Stroke Scale (NIHSS) (12) for the grading of stroke severity, which were evaluated during the period of intensive care. mRS (13) when evaluating dependency level according to stroke severity, Acute Physiology and Chronic Health Evaluation II (APACHE II) for prediction of mortality rates, Simplified Acute Physiology Score II (SAPS II) (14,15) and Sequential Organ Failure

Assessment Score (SOFA) (16) scales were examined and recorded in predicting mortality rates. All measurements were made within the first 24 hours.

Statistical Analysis: For statistical analysis, SPSS 25.0 (Statistical Package for the Social Sciences) program was used. Mean, median, lowest frequency, highest frequency and standard deviation (SD) were used in the descriptive statistics of the data. Kolmogorov-Smirnov test was used for normality distribution of variables. Student t test was used for normally distributed independent variables and Mann Whitney U test was used for non-parametric variables in the analysis between groups. Chi-square test was used in the analysis of qualitative data. A stepwise logistic regression analysis was used to identify independent predictors of intubation. Variables with probability value <0.10 in the univariate analysis and with clinical relevance were selected for the models. ROC analysis was used to calculate the optimal threshold value of the data obtained. In the comparison of the groups, a p value below 0.05 was considered significant.

RESULTS

Of 48 patients included, 13 (9 males, 4 females) had indications for intubation and followed up with invasive mechanic ventilation, 35 (12 males, 23 females) were followed up without intubation. The mean age of those who were intubated was $74,3 \pm 11,7$, and the mean age of those who were followed up without intubation was $71,7 \pm 13$ years. No significant statistical difference was found between the groups in terms of age and gender (Table 1). All cases were evaluated in terms of chronic disease histories and co-morbidities. There was no statistically significant relationship between the disease histories and comorbidities between two groups. All of the intubated patients were detected to have been intubated due to hypoxemia. In the intubated and non-intubated patients, GCS was $7,9 \pm 3,5$ and $13,6 \pm 2,4$ ($p < 0,001$, AUC: 0.895), NIHSS $15,7 \pm 8,2$ and $7,9 \pm 6$ ($p: 0,002$, AUC: 0.799), mRS $4,1 \pm 1,4$ and $2,8 \pm 1,5$ ($p: 0,007$), SAPS II $58,9 \pm 12$ and $25,6 \pm 10,7$ ($p < 0,001$, AUC: 0.973), APACHE II $18,6 \pm 4,1$ and $8,2 \pm 4,7$ ($p < 0,001$, AUC: 0.927), SOFA score $6,6 \pm 2$ and $2,2 \pm 1,9$ ($p < 0,001$, AUC: 0.931) (Table 1, Figure 2). When the patients who were intubated and not intubated were evaluated in terms of the etiology

Table 1. Baseline characteristics of the cases.

	not- intubated n:35	intubated n:13	p value
Demographics			
Age (years), mean (SD)	71,7 (13)	74,3 (11,7)	0,479
Female ^a	12 (34,3)	4 (30,8)	0,818
Comorbidities			
Hypertension	20 (57,8)	8 (61,5)	0,784
Diabetes mellitus	16 (45,7)	3 (23,1)	0,154
Cardiovascular diseases	6 (17,1)	2 (15,4)	0,885
Valvular heart disease	4 (11,4)	5 (38,5)	0,033
Atrial fibrillation	17 (48,6)	8 (61,5)	0,424
Cerebrovascular disease history	5 (14,3)	4 (30,8)	0,194
Transient ischemic attack	2 (5,7)	1 (7,7)	0,801
Admission severity scores			
GCS, mean (SD)	13,6 (2,4)	7,9 (3,5)	<0,001
NIHSS, mean (SD)	7,9 (6)	15,7 (7,2)	0,002
mRS, mean (SD)	2,8 (1,5)	4,1 (1,4)	0,007
SAPS II, mean (SD)	25,6 (10,7)	58,9 (12)	<0,001
APECHE II, mean (SD)	8,2 (4,7)	18,6 (4,1)	<0,001
SOFA, mean (SD)	2,2 (1,9)	6,6 (2)	<0,001
Admission labs			
White blood cell (*10 ⁹ /L), median (IQR)	8,0 (7,0-10,0)	10,6 (6,6-13,7)	0,241
Lymphocyte (*10 ⁹ /L), mean (SD)	2,05 (1,39)	1,24 (0,70)	0,020
Neutrophil (*10 ⁹ /L), median (IQR)	5,6 (4,1-7,1)	7,9 (4,9-11,1)	0,060
Hemoglobin (g/L), mean (SD)	13,8 (1,3)	13,8 (1,6)	0,981
Hematocrit (%), mean (SD)	41,7 (3,5)	42,2 (4,2)	0,578
Platelet count (*10 ⁹ /L), mean (SD)	223 (53)	222 (61)	0,807
Serum urea (mg/dL), median (IQR)	38,5 (33,0-46,0)	42,6 (29,5-74,7)	0,397
Serum creatinine (mmol/L), median (IQR)	0,96 (0,80-1,21)	1,06 (0,88-1,09)	0,780
Serum Glucose (mg/dL), median (IQR)	150 (110-204)	130 (118-192)	0,951
C-reactive protein (mg/L), median (IQR)	3,7 (2,0-11,2)	6,5 (4,6-58,0)	0,043
Serum Albumin (g/dL), mean (SD)	41,7 (3,5)	40,2 (6,7)	0,692
Red cell distribution width (%), median (IQR)	13,3 (12,9-14,2)	13,6 (12,8-14,6)	0,634
Mean platelet volume (fL), mean (SD)	10,2 (0,7)	10,5 (1,1)	0,736
Neutrophil/Lymphocyte, median (IQR)	3,0 (1,8-4,5)	6,1 (3,8-15,6)	0,011
Platelet/Lymphocyte, median (IQR)	120 (75-219)	185 (157-245)	0,042
TOAST			
Cardioembolic	18 (51,4) ^b	9 (69,2) ^b	
Large-artery atherosclerosis	5 (14,3) ^b	2 (15,4) ^b	
Small-vessel occlusion	2 (5,7) ^b	1 (7,7) ^b	
Undetermined etiology	10 (28,6) ^b	1 (7,7) ^b	0,493
Oxford classification (n.)			
TACI	5 (14,3)	8 (61,5)	0,001
PACI	19 (54,2)	1 (7,7)	0,004
POCI	6 (17,1)	4 (30,8)	0,302
LACI	5 (35,5)	0 (0)	0,150
Acute treatment			
tPA	9 (25,7)	1 (7,7)	0,172
Mechanical thrombectomy	2 (5,7)	2 (15,4)	0,281
Admission and follow-up information			
Application time to the hospital, mean (SD)	4,4 (3,6)	7,3 (6,0)	0,030
Intensive Care Hospitalization Period (Days), median (IQR)	5,0 (2,0-14,0)	11,0 (3,2-52,2)	0,103

Bold values indicate significance. **APECHE II:** Acute Physiology and Chronic Health Evaluation II, **GKS:** Glasgow Coma Score, **NIHSS:** National Institutes of Health Stroke Scale, **SAPS II:** Simplified Acute Physiology Score II, **SD:** Standard deviation, **SOFA:** Sequential Organ Failure Assessment Score, **TOAST:** Trial of Org 10172 in Acute Stroke Treatment, **LACI:** Lacunar infarct, **PACI:** Partial anterior circulation infarct, **POCI:** Posterior circulation infarct, **TACI:** Total anterior circulation infarct, **tPA:** tissue Plasminogen Activator.

^a Data are presented as number (%) unless otherwise specified

^b no significant difference between data with ^a

of stroke, cardio-embolic causes (n: 9, 69.2%-n: 18, 51.4%) were found to be the most common. Total anterior circulation infarction (TACI), rates were found to be significant in the intubated group. A significant difference was not detected between

lacunar cerebral infarct (LACI) (Table 1). When the patients followed up by intubation and without intubation were evaluated in terms of laboratory findings, a statistically significant difference were found between the values of lymphocyte, C-

reactive Protein (CRP), platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) (Table 1, Figure 3). The values of time in terms of hours of admission to the hospital after the event occurred was statistically significant. The mean intubation time was found to be 7.3 ± 6 days. (Table 1). As a result of multivariate analysis for predictive values for intubation, only SAPS II was found to be significant (Odds Ratio: 1.34, p : 0.047) (Table 2).

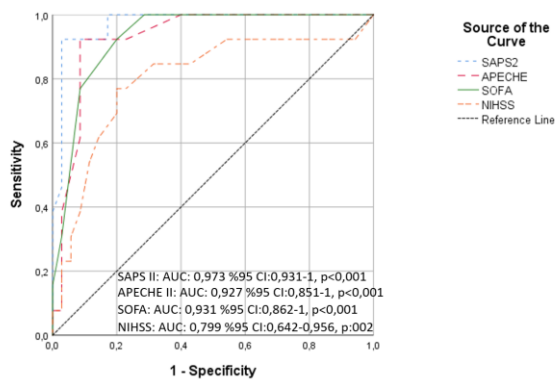


Figure 2. ROC analysis result of mortality and stroke severity scores.

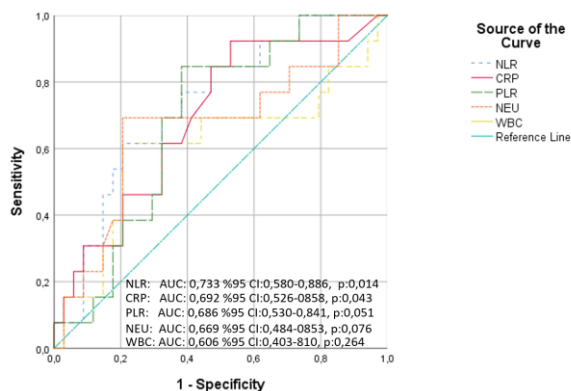


Figure 3. ROC analysis result of inflammatory parameters.

Table 2. Multivariate Analysis: Predictors of intubation.

Intubation	O. R	CI (%95)		p
		Upper	Lower	
SAPS II	1,34	1,003	1,794	0,047

DISCUSSION AND CONCLUSION

To the best of our knowledge, our study is the first study evaluating the relationship between mortality scores and inflammatory markers

evaluated in the early period of the event in AIS patients followed in the stroke ICU with the intubation prediction of these cases.

Although there was no difference between the groups in terms of chronic diseases and comorbidities, valvular heart disease was detected more in patients who were followed up by intubation. An increased risk of recurrent ischemic stroke in valvular heart disease is a known condition (17–19).

Although GCS score was used to predict prognosis in traumatic brain injuries (20), it was also used in the evaluation of consciousness and mortality associated with stroke (21). GCS values of ≤ 8 were considered as one of the intubation criteria, as it was thought to be associated with a decrease in the gag reflex and an increased risk of aspiration pneumonia (22–24). In our study, GCS scores were found to be lower in intubated cases ($p < 0.001$). The NIHSS score was developed to objectively evaluate the response to treatment in patients with AIS receiving thrombolytic therapy (12). Studies have shown that high NIHSS scores (threshold value > 13) are also associated with mortality in patients with ischemic stroke (25). In our study, NIHSS scores were significantly higher in intubated patients ($p = 0.002$) and the threshold value was detected as > 13 (AUC: 0.799). When the cases were evaluated in terms of mRS scores showing the dependent living index, mRS were significantly higher in intubated patients ($p: 0.007$). APACHE II and SAPS II scores predict mortality by taking age, disease histories, vital status, infection parameters, kidney function tests and lung status as criteria, regardless of the hospitalization diagnosis of intensive care patients (14,15). Although both the APACHE II and SAPS II systems can be used to measure performance in the ICU, Moon et al found that APACHE II in hemorrhagic stroke patients and SAPS II in ischemic stroke patients show a slightly better predictive of mortality (26). In our study, both APACHE II and SAPS II scores were higher in intubated cases and a statistical significance was found between the groups ($p < 0.001$). This finding indicates that APACHE II and SAPS II scores may predict the need for intubation in patients followed up in neurology intensive care with ischemic stroke (threshold value > 12.5 for APACHE II, and > 33 for SAPS II). In addition, our findings revealed that SAPS II (AUC: 0.973) scores could better predict the probability of intubation

in ischemic stroke patients than APACHE II (AUC: 0.927) scores. Safavi et al, determined that an APACHE II score above 12 predicted the need for mechanical ventilation in intensive care patients, similar to our study (27). Although APACHE II can predict intubation, it has been stated that it is not sufficient to predict prolonged intubation (28) and successful weaning (29). The SOFA score, which was previously used to evaluate sepsis-related organ failure has been used to evaluate organ failure in patients without sepsis over time (16). Although it is used for morbidity prediction rather than mortality prediction, it has also been shown to be associated with mortality. However, mortality prediction is not as strong as SAPS II or APACHE II (30). Semmlack et al stated that in patients followed up with status epilepticus, APACHE II, SAPS II and SOFA could predict mortality significantly, while APACHE II predicted it with the highest significance (31). Our study found that SOFA scores were statistically significant and high in intubated cases ($p < 0.001$) and the threshold value was found to be $> 3,5$ in the ROC analysis (AUC: 0.931). Therefore, SOFA score can be used as a predictor of intubation in cases followed in neurology ICU. However, As a result of multivariate analysis for predictive values for intubation, only SAPS II was found to be significant.

In our study, it was found that cardio-embolic causes constituted the etiological majority in both case groups and no statistically significant difference was found between the two groups in this respect.

In our study, the ratio of TACI ($p: 0.001$) in intubated cases, and the rate of PACI ($p: 0.004$) was statistically significantly higher in cases who were not intubated. It has been shown that TACI involvement is associated with high mortality and morbidity, and POCI involvement is associated with recurrent stroke (32).

Post-stroke neutrophil / lymphocyte ratio (NLR) is used as an inflammatory response marker to evaluate prognosis, with a threshold value ranging between 2.1 and 14 among studies (9,33,34). In a study where the NLR ratio was evaluated with meta-analysis, cases with a threshold value of > 4 were found to be associated with poor prognosis (8). In our study, the NLR ratio was found to be high in AIS patients who were intubated, and this was statistically significant ($p: 0.011$). We found the intubation

threshold value $> 4,93$ (AUC: 0,733). In addition, in our study, the PLR rate was statistically significantly higher in intubated cases ($p: 0,042$). With the capacity of platelets to respond and contribute to inflammation in the inflammatory process, they are involved in the underlying mechanism of tissue damage and organ dysfunction in various diseases such as cancer, sepsis, and cardiovascular diseases (35). Our findings reveal that both NLR and PLR values obtained in the early period of stroke from patients hospitalized in stroke intensive care with a diagnosis of AIS and intubation is not yet on the agenda can be used in predictive evaluations related to intubation.

In our study, CRP values were significantly higher in patients who were intubated ($p: 0.035$). CRP levels significantly increase in conditions such as injury, infection, and inflammation and are even considered a predictive marker in cardiovascular diseases (36). It has been shown as an independent marker of mortality in patients with ischemic stroke (37,38). Our current study finding, on the other hand, reveals that CRP values to be obtained in the early stages of AIS, when intubation is not on the agenda, can be used in predictive evaluations related to intubation.

Velissaris et al. showed that NLR and APACHE II, SAPS II, SOFA were correlated in patients followed up with sepsis in ICU. However, no significant correlation was found between admission CRP values and mortality scores (39). Usta et al. showed that there is a similarly significant correlation between the APACHE II score and NLR and PLR in patients followed in ICU (40). Also Altas et al. showed that PLR and NLR scores were able to predict mortality in ICU pneumonia patients like APACHE II and SOFA (41). In our study, NLR and PLR predicted intubation, but not as well as mortality scores.

In our study, 10 (76%) intubated cases were found to have died. The need for mechanical ventilation after stroke is an indicator of poor prognosis. The mortality rate due to mechanical ventilation ranges between 40-80% (7).

The main limitations of our study are its retrospective design, being conducted with a small number of patients, and being a single center study. Despite all this, the study data provided valuable information that the mortality scores and inflammatory markers evaluated in AIS patients can determine the relationship between these

cases and intubation prediction.

In conclusion, the patient and patient-related data in the early phase of AIS are influential on stroke outcomes. In the context of the study, it seems possible to use the mortality and morbidity prediction scores and inflammation parameters to be evaluated in the early period of stroke in patients presenting with AIS, to predict stroke-related intubation requirements. On the other hand, prospective and multi-center studies are required to reveal the specified parameters, post-stroke mortality and morbidity predictions, and to obtain clearer and more accurate data on stroke-related intubation and mechanical ventilation.

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Ethics

Ethics Committee Approval: The study was approved by Necmettin Erbakan University Ethical Committee (Number: 2020/2684, Date: 23.10.2020).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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