

## EREDETI KÖZLEMÉNY ORIGINAL ARTICLE

# Predictors of pneumonia in stroke patients with dysphagia: A Turkish study

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**Background and purpose** – Dysphagia, characterized by difficulty in swallowing due to neurological deficits, stands out as the foremost contributor to stroke associated pneumonia (SAP) development. Recent investigations have explored the utility of blood tests, including parameters like neutrophil count, leukocyte count, neutrophil-tolymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the CRP to albumin ratio (CAR), at the time of admission as potential markers for predicting SAP development. This study is set out to assess predictors of SAP in patients with acute ischemic stroke and dysphagia.

**Methods** – This retrospective cross-sectional study, conducted at the University of Health Sciences, Neurology Department of Erenkoy Mental Health Neurological Disorders in Istanbul, Turkey, between January 2021 and January 2023, assessed 65 individuals with acute ischemic stroke and dysphagia. Excluding specific criteria, clinical and laboratory data were collected. Patients were categorized into SAP and non-SAP groups based on diagnostic criteria. Results provide insights into risk factors of SAP.

**Results** – In this study of 65 stroke patients with dysphagia, 27 (41.5%) developed SAP within the first week. No significant differences in age, gender, comorbidities, or infarct size were observed between the pneumoniapositive and pneumonia-negative groups (p > 0.05). HbA1c levels were significantly lower in the pneumonia-positive group (p = 0.02). Logistic regression revealed that NLR, CAR levels, and the presence of atrial fibrillation (AF) were significant predictors of pneumonia development (p < 0.001). A tüdőgyulladás előrejelzői dysphagiás stroke-betegekben: Egy török tanulmány Kaşikçi HÖ, MD; Üçgül Erçin E; Karaci R, MD; Mustafa Ülker M, MD; Mayda Domaç F, MD

Háttér és cél – A neurológiai deficit miatt fellépő nyelési nehézségekkel jellemezhető dysphagia a stroke-hoz társuló tüdőgyulladás (stroke associated pneumonia, SAP) kialakulásának egyik legfontosabb oka. A közelmúltban végzett vizsgálatok feltárták a vérvizsgálat, ezen belül az olyan paraméterek, mint a neutrophilszám, a leukocytaszám, a neutrophilek és lymphocyták aránya (neutrophil-to-lymphocyte ratio, NLR), a thrombocyták és lymphocyták aránya, valamint a C-reaktív protein és az albumin aránya (CRP to albumin ratio, CAR) ismeretének hasznosságát a kórházi felvételkor, mivel ezek a SAP kialakulásának előrejelzésére szolgáló potenciális markerek lehetnek. E tanulmány célja, hogy felmérje a SAP prediktorait akut ischaemiás stroke-ban és dysphagiában szenvedő betegeknél.

Módszerek – A törökországi Isztambulban, az Egészségtudományi Egyetem Erenkoy Mentális Egészség és Neurológiai Rendellenességek Neurológiai Osztályán 2021 januárja és 2023 januárja között végzett retrospektív keresztmetszeti vizsgálatunkban 65, akut ischaemiás stroke-ban és dysphagiában szenvedő személy adatait tekintettük át. Specifikus kritériumok alkalmazásával klinikai és laboratóriumi adatokat gyűjtöttünk. A betegeket a diagnosztikai kritériumok alapján SAP- és nem SAP-csoportba soroltuk. Az eredmények betekintést nyújtanak a SAP kockázati tényezőibe.

**Eredmények** – A vizsgálatban 65 dysphagiás stroke-betegből 27 (41,5%) betegnél alakult ki SAP az első héten. A tüdőgyulladáspozitív és a tüdőgyulladás-negatív csoport között nem volt szignifikáns különbség az életkor, a nem, a társbetegségek vagy az **Conclusion** – Dysphagia is considered one of the most significant risk factors for SAP. However not all ischemic stroke patients with dysphagia develop SAP; that is the reason we think NLR, CAR, and AF might be predictors of SAP in acute ischemic stroke patients with dysphagia. infarktusméret tekintetében (p > 0,05). A HbA<sub>1c</sub>-szintek szignifikánsan alacsonyabbak voltak a pneumoniapozitív csoportban (p = 0,02). A logisztikus regresszió kimutatta, hogy az NLR- és a CAR-szintek, valamint a pitvarfibrilláció (atrial fibrillation, AF) szignifikáns előrejelzői a tüdőgyulladásnak (p < 0,001).

Következtetés – A dysphagia a SAP egyik legjelentősebb kockázati tényezője. Azonban nem minden ischaemiás stroke-os betegnél alakul ki SAP; ezért úgy gondoljuk, hogy az NLR, a CAR és az AF a SAP prediktora lehet a dysphagiás akut ischaemiás stroke-os betegeknél.

**Keywords:** stroke, dysphagia, pneumonia, infection, stroke associated pneumonia

Kulcsszavak: stroke, dysphagia, pneumonia, infekció, stroke-hoz társuló tüdőgyulladás

**S** troke-associated pneumonia (SAP) is one of the most common complications of stroke and typically develops within the first week after a stroke<sup>1</sup>. There are many factors that impact SAP development; current predictive models mainly focus on dysphagia, age, comorbidities, and gender<sup>1</sup>. Even though there are many models, there is still no widely accepted model for clinical use.

SAP typically occurs as aspiration pneumonia. Based on our knowledge, the immune system also plays a role in the pathogenesis of SAP. Immunosuppression associated with cholinergic pathways, functional loss of T cells, and an increase in activity of sympathetic pathways have been linked to a higher risk of infection<sup>2, 3</sup>. SAP leads to increased mortality and morbidity, resulting in prolonged hospital stays for patients<sup>4</sup>.

A widely accepted idea is that the nervous system plays a significant role in regulating the body's overall immune function. In the context of a stroke, brain injury triggers the activation of neurogenic pathways, including the sympathetic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the parasympathetic nervous system, which collaborate to impact the strength and extent of the body's immune response<sup>5</sup>.

It is generally admitted that stroke itself has an important relationship with inflammation. Recognizing high-risk unstable inflamed atherosclerotic plaques may aid in identifying individuals with asymptomatic carotid stenosis who could potentially benefit from procedures like endarterectomy or carotid artery stenting, or those requiring intensive anti-inflammatory treatments. In the context of carotid atherosclerosis, numerous investigations have indicated a connection between inflammation and various indicators of plaque instability with recent symptoms and cerebral events. For instance, a study involving 269 patients with carotid plaques revealed that ruptured plaques in individuals who had experienced a stroke showed higher levels of monocyte/macrophage and T-cell infiltration when compared to asymptomatic or transient ischemic attack (TIA) patients<sup>6</sup>.

Dysphagia caused by a neurological deficit is the most common factor in the development of SAP. More than half of stroke patients are affected by dysphagia. In most cases, it improves over time, but in 11-13% of them continues to persist longer than 6 months7. Weak swallowing and coughing reflexes, caused by a neurological deficit, result in the aspiration of particles. Apart from a nasogastric tube is not always effective in preventing aspiration pneumonia, aspiration can happen due to small volumes of pharyngeal and gastric content. If oral intake is insufficient, liquid nutritional supplements are suggested to meet energy and protein requirements. In cases where oral feeding is not possible, early enteral nutrition should be initiated within 48 hours. Exclusive enteral nutrition preserves gastrointestinal function and structure, supporting the immune system and modulating the metabolic response, thereby improving survival<sup>8</sup>.

Not all patients with dysphagia develop SAP and vice versa. Different scoring systems (A2DS2, AISAPS, ISAN) have been designed to predict the risk of SAP<sup>9</sup>. However, they are not generally accepted in clinical use, and none of the previous studies include only patients with dysphagia and determine which patients are more likely to develop SAP. Therefore determining a biological marker to find a relationship with a comorbidity can help the clinicians to precede and prevent SAP in patients with dysphagia. The concept of finding an inflammato-

ry marker in acute ischemic stroke patients is popular; a study has been conducted with the conclusion that the prevalence of CD64+ neutrophils suggests a biphasic alteration in the immune response post-ischemic stroke showing a decrease below baseline after one week in patients without infection<sup>10</sup>. This finding suggests that CD64+ neutrophils could serve as a reliable marker for identifying the evolving inflammatory response related to infection following a stroke.

Although dysphagia is an important risk factor of SAP, it does not cause pneumonia in more than 67% of stroke patients<sup>7</sup>. A high National Institutes of Health Stroke Scale (NIHSS) score upon hospital admission, severe dysphagia, atrial fibrillation (AF), and anterior circulation infarcts are more frequently associated with SAP<sup>11</sup>.

A recently published review and a study have investigated whether blood tests, such as neutrophil count, leukocyte count, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-Reactive Protein (CRP) to albumin ratio (CAR) at the time of admission, can serve as markers for pneumonia development<sup>12, 13</sup>. NLR is a cost-effective and readily accessible biomarker, reflecting the equilibrium between acute and chronic inflammation as well as adaptive immunity. Although specific threshold values are yet to be established, variations in NLR over time indicate potential disruptions in the immune system. Also, during the COVID-19 pandemic, the CAR was also shown in a multivariate analysis study in COVID patients to be statistically significant for the risk of intensive care admission over the age of 65. Elevated CAR is believed to have utility in forecasting the severity of COVID-19, the duration of hospitalization, and mortality rates<sup>14</sup>.

In addition, a relationship between SAP and stress hyperglycaemia (ratio of blood sugar levels to HbA1c values) has been suggested by *Tao* and colleagues<sup>15</sup>. These tests reflect systemic inflammatory responses.

There are some studies suggesting the use of prophylactic antibiotic therapy in patients with ischemic stroke, but the guidelines do not recommend this approach<sup>16, 17</sup>. Predicting which stroke patients will develop pneumonia is pivotal for prevention. The purpose of our study is to identify predictors of SAP in patients with acute ischemic stroke and dysphagia.

# Materials and methods

### Study population

This cross-sectional study retrospectively evaluated 65 individuals hospitalized between January 2021 and January 2023 at the Neurology Department of Erenkoy Mental Health Neurological Disorders in Istanbul, Turkey. Acute ischemic stroke patients with dysphagia were admitted to our clinic and evaluated. Patients below the age of 18, who did not have an ischemic etiology, had other inflammatory, rheumatological, or systemic diseases that could affect blood tests, who developed an infection other than pneumonia during their hospital stay, who developed haemorrhagic transformation, patients without dysphagia, and patients who were admitted in our clinic after 24 hours of stroke onset were excluded. Totally 395 patients with acute ischemic stroke were examined and due to the exclusion criteria 330 patients were not included, therefore the study was conducted with 65 patients.

#### Methods

The clinical and demographic data of the patients were recorded. Neurological examination, and the following information were documented: NIHSS score, presence of AF, use of beta blockers, iron levels, neutrophil count, leukocyte count, lymphocyte count, platelet count, glucose levels, CRP and albumin levels, HbA1c, NLR, PLR, CAR, stress hyperglycaemia and size of infarct (infarcts smaller than 3 cm in diameter were classified as small infarcts)<sup>18</sup>. The Bedside Swallowing Test had been performed to assess dysphagia. During their hospital stay patients were examined by a language and speech therapist.

Patients were divided into two subgroups: those who developed SAP and those who did not. While there are no consensus criteria for the diagnosis of SAP, our study applied the criteria suggested by *Smith* et al<sup>19</sup>, which include progressively infiltrating lesions in post-stroke chest images, as well as the presence of more than two of the following clinical symptoms of infection: fever of 38 °C or higher; newly occurring cough, productive cough, or worsening of preexisting respiratory disease symptoms with or without chest pain; signs of pulmonary consolidation and/or moist rales; and peripheral white blood cell count above  $10 \times 109/L$  or below  $4 \times 109/L$ .

### Statistical analysis

For statistical evaluation and data processing, we used SPSS version 26. Descriptive statistics, such as mean, median, standard deviation, minimum values, maximum values, and the 25<sup>th</sup> and 75<sup>th</sup> percentiles of data were calculated. The normality of the data was determined using the Shapiro-Wilk test. The Mann-Whitney U test was used to evaluate non-normally distributed data. Chi-square test or Fisher's exact test were used in order to compare categorical variables in different groups. Logistic regression analysis was performed to identify predictive factors for the development of SAP. A significance level of 5% was used for type-1 error in statistical analysis. In all tests, a p-value of less than 0.05 was considered statistically significant. The study was approved by the ethical committee of Erenkoy Mental Health&Neurological Disorders.

	Median	Minimum	Maximum	Mean	Std. Deviation
Age	73	41	95	72.44	10.02
Admission NIHSS score	8	1	22	9.03	22.31
CRP (mg/dL)	1.30	0	14.50	2.36	2.74
Albumin (g/L)	3.80	1.67	5.12	3.79	0.53
CRP/Albumin Ratio (*100)	0.30	0	4.99	0.69	0.94
Stress hyperglycemia ratio	18.40	9.47	32.31	18.94	4.88
Glucose (mg/dL)	109.00	73.54	280.00	123.08	42.55
HBA <sub>1c</sub> (mmol/mol)	5.90	4.90	16.60	6.64	2.09
Neutrophil/lymphocyte Ratio	3.13	0.19	31.36	4.25	4.30
Platelet/lymphocyte Ratio	127.77	10.90	374.19	140.03	64.05
Neutrophil count (x10^3/uL)	6.13	2.59	20.70	6.42	2.73
Lymphocyte count (x10^3/uL)	1.73	0.62	4.60	1.91	0.77
Platelet count (x10^3/uL)	233.00	148.00	437.00	240.00	62.02
Iron Level (ug/dL)	54.51	9.00	148.06	56.42	29.05

#### Table 1. Total patient group results

## Results

Sixty-five patients were included in the study. 34 patients (52.39%) were female and 31 were male. The mean age of the patients' was  $72.44 \pm 10.02$  years. Within the first week of stroke 27 of them (41.5%) developed SAP. There was no statistically significant difference between the pneumonia-positive group and pneumonia-negative group in terms of age (p=0.20) and gender (p=0.95). Out of 65 patients, 20 (30.76%) had diabetes mellitus, 43 (66.15%) had hypertension, 23 (35.38%) had chronic heart disease, 20 (30.76%) had a previous history of cerebrovascular events, and 11 (16.92%) of them used beta blockers. There was no statistically significant difference between the pneumonia-positive and the pneumonia-negative groups in terms of beta blocker use (p=0.10), hypertension (p=0.94), diabetes mellitus (p=0.20), chronic heart disease (p=0.44), previous history of cerebrovascular event (p=0.35), and size of infarct (p=0.14).

The patients' NIHSS scores were calculated upon admission as it is seen in **Table 1**. The mean NIHSS score in the pneumonia-positive group was  $8.62 \pm 4.49$ , while the mean value was  $9.31 \pm 4.92$  in the pneumonia-negative group. No statistically significant difference was detected between the NIHSS score and the development of pneumonia (p=0.70). Statistical difference analysis between SAP group and non-SAP group is seen in **Table 2** using Mann-Whitney U test.

At the time of hospital admission, it was discovered that 23 patients (35.40%) had an electrolyte imbalance. There was no significant difference found between the two groups (p=0.81). Median HbA<sub>1c</sub> level was 5.60  $\mu$ g/dL in the pneumonia positive group, while 6.20  $\mu$ g/dL in the pneumonia negative group. The difference in HbA1c levels was statistically significant (p=0.02), but it's important to question how relevant this difference is in real-world medical situations.

The median blood glucose level was 104.48 mg/dL in

Table 2. Statistical difference analysis between SAP group and non-SAP group using Mann-Whitney U test

	ADMISSION NIHSS	CRP	ALB	CAR	SHR	NLR	PLR	LMR	GLUCOSE	HBA1C
Mann- Whitney U	485.000	494.500	372.000	424.000	410.000	444.500	507.000	307.000	361.500	292.000
Wilcoxon W	863.000	1235.500	723.000	1019.000	761.000	1185.500	1248.000	685.000	739.500	643.000
Z	-374	246	871	269	477	912	080	-1.180	-2.017	-2.241
Asymp. Sig. (2-tailed)	.709	.805	.384	.788	.633	.362	.936	.238	.044	0.025
*p<0.05										

	B - S.E.	Sig. (p value)	Exp(B)	95% C.l. for EXP(B) (Lower - Upper)
PLR	-0.027 - 0.014	0.055	0.974	0.947 - 1.001
NLR	1.009 - 0.390	0.010*	2.743	1.277 – 5.894
NMR	-0.130 - 0.106	0.217	0.878	0.714 - 1.079
LMR	-0.70 - 0.101	0.490	0.933	0.765 – 1.137
SHR	-0.149 - 0.093	0.110	0.862	0.718 - 1.034
CAR	1.180 - 0.525	0.025*	3.255	1.163 – 9.106
Beta Blocker Usage	-2.662 - 1.498	0.076	0.070	0.004 - 1.315
Size of Lesion	-0.894 - 0.891	0.316	0.409	0.071 – 2.344
Presence of AF	2.727 - 0.977	0.005*	15.281	2.252 - 103.676

#### Table 3. Regression analysis of the predictors

\*p < 0.05

p < 0.001, -2 Log likelihood=37.847, Cox Snell R<sup>2</sup>=0.450, Nagelkerke R<sup>2</sup>=0.600. Hosmer-Lemeshow  $\chi^2$  (8) = 4.798, p > 0.05

the pneumonia-positive group and 117.50 mg/dL in the negative group. The 25th percentile and the 75th percentile of blood glucose levels were 92.00 mg/dL and 118.09 mg/dL in the pneumonia positive group, while they were 97.50 mg/dL and 156.50 mg/dL in the pneumonia negative group. The p-value was 0.44. Logistic regression analysis was conducted to identify the risk factors for the development of pneumonia. In the created model, the following factors were included: presence of AF, usage of beta-blockers, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), neutrophil-to-monocyte ratio (NMR), stress hyperglycemia ratio, CRP to albumin ratio, and size of the lesion. The result of the regression analysis as it can be seen in Table 3, indicated that the predictors collectively significantly predicted the outcome (P < 0.001, Nagelkerke  $R^2 = 0.600$ ). The goodness of fit of the models was assessed using the Hosmer-Lemeshow test ( $\chi^2$ : (8) = 4.798, p > 0.05). The analysis determined that NLR (odds ratio [OR]: 2.743, 95% CI: 1.277 - 5.894), CAR levels (odds ratio [OR]: 3.255, 95% CI: 1.163 – 9.106), and the presence of atrial fibrillation (OR: 15.281, 95% CI: 2.252 - 103.676) significantly predicted the risk of pneumonia.

# Discussion

The aim of this cross-sectional study was to assess an efficient and clinically useful marker for predicting the development of SAP in patients with dysphagia. Stroke stands as the primary neurological factor behind dysphagia, marked by difficulties in swallowing. Between 42% and 67% of stroke patients experience dysphagia within three days of the event. Of those, half face aspiration, and a third of aspirating patients develop pneumonia requiring treatment. Early identification of dysphagia and

aspiration risk is crucial for stroke patients. Regarding the nutritional treatment of individuals with acute stroke, there are established guidelines from both international and Hungarian professional sources. The fundamental concept underscores the importance of identifying challenges in swallowing, as this serves as the foundation for applying suitable nutritional approaches<sup>20</sup>. It is recommended to conduct swallowing screening at the earliest possible stage for all stroke patients. Stroke patients with dysphagia not only face the risk of aspiration and pneumonia, but also dehydration, malnutrition, weight loss, risk of other infectious diseases and death. Therefore it is important to find predictors to assess which patient with dysphagia has the susceptibility to develop the mentioned diseases.

For our limitations, the relatively small sample size of 65 patients in our study may restrict the generalizability of our results to a larger stroke population. That is the reason why caution should be done when extending the results to a wider demographic pool. The absence of detailed information on the brain lesion location limits the comprehensiveness of our study. Understanding the influence of lesion location could offer a more nuanced interpretation of the factors that contribute to the development of SAP. In addition, without a long-term follow-up data after the initial stroke, our understanding of the progression of dysphagia and speech-language deficits is restricted. Observation for a longer time would allow us to have important insights into the lasting impact and changes of these complications. Though we acknowledge these limitations, they emphasize the urgency for future research to involve larger, multicentre cohorts to improve the external validity of our findings.

We found that patients with higher CRP/albumin ratio were more likely to develop SAP. In the pneumonia-pos-

itive group the median CAR ratio was 0.35, while it was 0.31 in the pneumonia-negative group. Circulating CRP and albumin are recognized biomarkers of systemic inflammation. The CRP to albumin ratio (CAR), a new-ly introduced biomarker, has been proposed as a more dependable indicator of inflammatory conditions when compared to either CRP or albumin on their own<sup>21</sup>.

It was also found in our study that a higher neutrophil-to-lymphocyte ratio was present in the pneumonia-positive group. This biomarker effectively integrates two aspects of the immune system: the innate immune response, primarily driven by neutrophils, and the adaptive immune response. NLR is widely recognized for its predictive significance and is associated with mortality both in the overall population and in various distinct groups of conditions such as sepsis, pneumonia, COVID-19, and cancer<sup>22</sup>. In a study involving 3,340 patients with community-acquired pneumonia, NLR was found to be a promising marker for predicting outcomes<sup>12</sup>. While many studies concentrate on the relationship between NLR and mortality prediction, there are not many studies that consider NLR as a predictor of the development of infection<sup>23</sup>. On the other hand, there are some studies indicating that NLR can be used for the early identification of severe SAP and to predict ICU admission in patients with intracerebral hemorrhage<sup>24</sup>. Our results indicated that NLR is a predictor of SAP in patients with ischemic stroke and dysphagia.

PLR is thought to be another potential marker of stroke severity because of its ability to encompass both inflammatory and thrombotic pathways, making it a more valuable indicator than relying solely on platelet or lymphocyte counts. In a study it is suggested that PLR increases in acute ischemic stroke patients as well as it correlates with NIHSS score<sup>25</sup>. However, we did not find a significant correlation between SAP development and PLR levels. The predictive value of an increased PLR has been extensively researched in multiple medical conditions, including cardiovascular disease and cancer, for indicating unfavorable outcomes. Nevertheless, its role as a prognostic factor for stroke patients, particularly those with ischemic strokes, remains uncertain<sup>26</sup>.

Atrial fibrillation has a complicated relationship with inflammation. Whether AF is the cause or the result of the process still remains unclear. Current data demonstrates that AF has the capacity to induce inflammation and provoke structural alterations in the myocardium. Moreover, this inflammation and structural transformation collaboratively contribute to lowering the threshold for the onset of AF<sup>27</sup>. AF remained a significant risk factor for SAP development in ischemic patients with dysphagia. As indicated by previous SAP prediction models such as the A2DS2 score (age, atrial fibrillation, dysphagia, sex, and stroke severity), AF was identified as a potential predictor of SAP<sup>4</sup>. As an interesting result in our study, we found that  $HbA_{1c}$  and blood glucose levels were higher in the pneumonia negative group. Considering that elevated HbA1c levels are typically associated with infections, the contentious outcome of our study raises questions. Our research, even though it shows a controversial result, lays the groundwork for future studies to explore the practical significance of HbA1c variations in relation to pneumonia. This provides useful perspectives on its possible use as a prognostic or diagnostic indicator.

In our study the SHR ratio did not show any statistically significant difference between the two groups. In contrast to our results, a study conducted on a cohort of 2039 patients found that higher SHR levels were significantly associated with an increased risk of SAP in stroke patients. However, this effect was primarily observed in patients without diabetes. Therefore the relationship between SAP and SHR still needs to be investigated<sup>15</sup>.

Elevated sympathetic activity following a stroke plays a role in the development of various complications, including post-stroke immune suppression. It has been proposed that treatment with  $\beta$ -blockers is neuroprotective and can reduce the occurrence of infectious complications following a stroke<sup>28</sup>. Notably, a study involving 625 patients, of whom 553 were admitted with acute ischemic stroke and 72 with intracerebral hemorrhage, found that exposure to  $\beta$ -blockers, which means taking  $\beta$ -blockers before a stroke and continuing the treatment during hospitalization, did not lower the risk of stroke-related pneumonia. However, it did result in a decrease in the occurrence of urinary tract infections<sup>29</sup>. That being said, another meta-analysis shows an increase in post-stroke infections associated with β-blocker treatment. In our study there was no correlation between SAP development and  $\beta$ -blocker use, therefore more data is essential for this subject as well<sup>30</sup>.

Another subject that needs to be discussed is the size of the infarct and the lack of statistically significant difference in NIHSS scores between the pneumonia-positive and pneumonia-negative groups in our study. NIHSS score is also a component of ISAN predictor model: prestroke Independence [modified Rankin scale], Sex, Age, National Institutes of Health Stroke Scale. ISAN model is believed to be a tool in SAP prediction and clinical use; but the same study also noted that external validation was required in ischemic and hemorrhagic stroke cohorts<sup>31</sup>. With our patient group having moderate NIHSS scores, it is predictable that the two groups may not differ statistically.

Our study did not show any statistically significant difference in lesion size between the two groups. To explain that, it is important to emphasize that the location of brain lesions were not recorded in the study. In a study of 592 patients with acute stroke, it was found that strokes in the territory of the left anterior cerebral artery were associated with pneumonia<sup>32</sup>. In another study, it was observed that the size of the infarct was the primary factor associated with lymphocytopenia on day 1 and day 4 after a stroke. This was accompanied by a decrease in natural killer cell counts and an increase in monocyte counts, followed by dysfunction of monocyte cells after extensive infarcts<sup>33</sup>.

Lastly, regular monitoring of NLR and CAR in patients with dysphagia post-stroke could serve as a cost-effective and accessible strategy for identifying those at increased risk of SAP. Clinicians could effortlessly incorporate these markers into routine assessments, especially in the early post-stroke phase. Also given the fact that AF should already be kept in mind as a stroke risk factor and needs to be investigated in all stroke patients, it is important to take into consideration that stroke patients with atrial fibrillation could be more likely to develop SAP.

# Conclusion

Dysphagia is considered as one of the most significant risk factors for SAP. However, there is a lack of published studies that specifically aim to determine which patients with dysphagia are more likely to develop SAP. According to our knowledge, there is no existing research exploring these variables in this specific patient population. Therefore we think that especially NLR, CAR, and AF might be predictors of SAP in acute ischemic stroke patients with dysphagia. If further validated in larger and more diverse patient cohorts, these markers might offer valuable insights for clinicians in risk assessment and personalized interventions.

CONFLICT OF INTEREST – The authors declare no conflict of interest.

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