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Predicting 6-month modified Rankin Scale score in stroke patients

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Abstract: The study aimed to identify predictors of 6-month outcomes in acute ischemic stroke (AIS) patients using the modified Rankin Scale (mRS). A prospective observational cohort study was conducted on 277 AIS patients admitted to the Neurology Departments of Cluj-Napoca Emergency County Clinical Hospital between December 2020 and July 2021. After excluding those lost to follow-up or who withdrew due to COVID-19 concerns, 121 patients were followed for six months. Data collected included demographic details, clinical assessments (including NIHSS and mRS scores), laboratory tests, and imaging results. The study found significant differences between patients with mild/moderate disability (mRS 0-3) and those with severe disability (mRS 4-5) at six months. Age, heart failure, NIHSS score, resistin levels, C-reactive protein, and lesion volume were significantly associated with worse outcomes. Multivariate logistic regression revealed that heart failure was an independent predictor of severe disability, increasing the risk by over seven times. Specific clinical and biochemical markers at admission may be able to predict long-term functional outcomes in AIS patients, which may inform individualized patient management and rehabilitation strategies.

Keywords: acute ischemic stroke, modified Rankin Scale score, disability, prediction

1. Introduction

Stroke remains a leading cause of mortality and long-term disability worldwide, with acute ischemic stroke (AIS) accounting for approximately 85% of all stroke cases[1]. The modified Rankin Scale (mRS) is a widely used tool for assessing the degree of disability or dependence in daily activities following a stroke. The mRS, which ranges from 0 (no symptoms) to 6 (death), is instrumental in both clinical practice and research for evaluating stroke outcomes and the effectiveness of interventions[2].
Predicting the functional outcomes of stroke patients is extremely important in order to tailor post-stroke care and rehabilitation. Identifying early predictors of disability can aid in optimizing treatment strategies, improving patient prognosis, and allocating

healthcare resources more effectively[3–5]. Several factors have been investigated as potential predictors of mRS scores at six months post-stroke, including demographic characteristics, clinical presentations, laboratory markers, and neuroimaging findings [6,7]. Age is a well-established determinant of stroke outcomes, with older age being consistently associated with worse functional recovery [8]. The severity of the stroke at onset, commonly assessed using the National Institutes of Health Stroke Scale (NIHSS), is another critical predictor of long-term outcomes [9]. Higher NIHSS scores, indicating more severe strokes, are correlated with higher mRS scores at follow-up, reflecting greater disability[10]. Comorbidities such as arterial hypertension (AH), diabetes mellites (DM), and heart failure (HF) have been implicated in poorer outcomes, likely due to their contribution to both the severity of the initial stroke and the patient's overall resilience to recovery[11,12].

While several predictive models for stroke outcomes, such as the ASTRAL, DRAGON, SEDAN or other scores, have been developed, these models often overlook the potential impact of emerging biomarkers like resistin[13–15]. Several biomarkers have been studied for their potential role in predicting stroke outcomes. Elevated levels of inflammatory markers, such as C-reactive protein (CRP), have been associated with worse prognosis, possibly due to their reflection of underlying systemic inflammation, which could exacerbate stroke-related damage[16]. Adipokines, including leptin and resistin, are another area of interest. These hormones, produced by adipose tissue, are involved in inflammatory processes and have been linked to cardiovascular diseases, including stroke [17–19]. . Resistin, an adipokine associated with inflammation and insulin resistance, has garnered increasing attention in recent years for its potential role in stroke outcomes. Elevated resistin levels have been implicated in the pathophysiology of various cardiovascular diseases, including stroke, due to its pro-inflammatory effects. Recent studies have produced mixed results regarding the role of resistin in stroke short- or long-term prognosis, with some suggesting it exacerbates outcomes, while others find no significant association [19–24]. This study seeks to address these inconsistencies by integrating resistin levels with established clinical and imaging predictors.

Neuroimaging provides additional insights into stroke prognosis. The volume of the ischemic lesion, as measured by techniques like computed tomography (CT) or magnetic resonance imaging (MRI), has been shown to correlate with functional outcomes[5,25,26]. Larger lesion volumes are generally associated with more significant neurological deficits and higher mRS scores[27]. The presence of carotid plaques, identified through ultrasound, is another factor that may influence stroke outcomes, as it reflects the extent of atherosclerotic disease, which can predispose patients to recurrent strokes and impede recovery[28].

This study aims to identify the factors that predict mRS scores at six months post-AIS, by integrating both established and new predictors of stroke outcomes in order to advance current knowledge. By focusing on biomarkers like resistin, which have shown variable associations with stroke recovery, we seek to clarify their role and improve the predictive accuracy of existing models. By understanding these predictors, healthcare providers can better anticipate patient needs and improve long-term care strategies for stroke survivors.

2. Materials and Methods

We conducted a prospective, observational, analytical cohort study, in which we consecutively enrolled 277 patients admitted for acute ischemic stroke (AIS) to the Neurology Departments of Cluj-Napoca Emergency County Clinical Hospital between 1 December 2020 and 15 July 2021. Of these, only 244 patients who survived and were discharged were ultimately included. Subsequently, 66 patients were lost to follow-up,

either due to not attending the 6-month follow-up consultation (51 patients) or because of death after discharge (15 patients). Additionally, 57 patients withdrew from the study due to fear of contracting COVID-19 infection. Therefore, the final cohort consisted of a total of 121 patients which were followed for six months.

The diagnosis of AIS was based on clinical assessment and cerebral imaging by non-injected computed tomography. The study was conducted in compliance with the principles of the Declaration of Helsinki, and the protocol of our study obtained authorization from the Ethics Committee of Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania (Approval No. 278/11.08.2020).

The following inclusion criteria were set: age over 18 years, AIS confirmed by cerebral computer tomography imaging, and informed consent provided by the patient or their legal representatives. Patients who passed away during hospitalization, or within six months of discharge, diagnosed with COVID-19 infection, sepsis, neoplastic conditions, documented cognitive disorders, autoimmune disorders, or whose follow-up cerebral imaging ruled out ischemic stroke diagnosis, were excluded.

Upon admission, all patients were subjected to a meticulous anamnesis or heteroanamnesis, underwent neurological examination by an expert neurologist, and had calculated their National Institute of Health Stroke Scale (NIHSS), that assesses the severity of the stroke. A full clinical examination was performed, including body mass index (BMI) measurement. Demographic data, cardiovascular risk factors, comorbidities and laboratory tests (leptin, resistin, C-reactive protein (CRP) were recorded.

Carotid plaques were identified by ultrasound examination. The ischemic strokes were categorized by etiology using the TOAST classification (Trial of Org 10172 in Acute Stroke Treatment), in atherothrombotic, cardioembolic, small vessel disease, undetermined etiology, and other determined etiologies. Ischemic lesion volume was estimated utilizing the ellipsoid volume equation $V=4/3\ \pi\times(A/2)\times(B/2)\times(C/2)$ with A denoting the largest axial diameter, B the axial diameter perpendicular to A, and C the craniocaudal diameter. This study measured the volume of ischemic lesions using CT scans. The choice of CT over other modalities like MRI was driven by its widespread availability and rapid acquisition, which is critical in the acute stroke setting. The selection of lesion volume as a key variable was based on literature evidences linking larger ischemic lesions to worse functional outcomes. Previous studies have consistently demonstrated that lesion size correlates strongly with the extent of neurological impairment and recovery potential[25,27]. Therefore, assessing lesion volume was integral to our objective of predicting long-term disability, as it directly measures the initial brain injury.

The blood samples were collected in ethylenediaminetetraacetic acid (EDTA) and biochemistry tubes with the routine blood the next morning after admission. lasma levels of resistin (code: RD191016100) and leptin (code: RD191001100) were quantified using commercially available ELISA kits (BioVendor R&D, Brno, Czech Republic). Resistin was chosen due to its established role in inflammation and insulin resistance, which are critical in cardiovascular diseases, including stroke. Elevated resistin levels have been associated with poor outcomes in various cardiovascular conditions, making it a candidate for predicting stroke severity and recovery. The choice to include resistin was also motivated by emerging evidence suggesting its role in exacerbating ischemic injury through pro-inflammatory mechanisms, although previous findings have been inconclusive[17,18,29,30]. Leptin, another adipokine, was included due to its dual role

in metabolic regulation and inflammation. While primarily recognized for its role in obesity and metabolic disorders, leptin has also been implicated in modulating inflammatory responses, which could influence stroke recovery. Its inclusion aimed to explore its potential additive value to the predictive factors [31–33].

For each patient, the following scores assessing functional limitations were calculated: functional deficits were measured using the Modified Rankin Scale (mRS) at admission and 6 months post-stroke. The modified Rankin Scale (mRS) measures the level of disability or dependence in daily activities after an acute ischemic stroke, with scores ranging from 0 (no symptoms) to 6 (death) where higher scores indicate greater impairment. It is a key tool to assess functional outcomes and planning post-stroke care [2,34].

The statistical analysis in this study was conducted using MedCalc® Statistical Software version 22.021 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2024)). Descriptive statistics were utilized to summarize the demographic and clinical characteristics of the study population. Continuous variables were expressed as medians with interquartile ranges due to non-normal distribution, while categorical variables were presented as absolute numbers and percentages. The primary outcome of interest was the modified Rankin Scale (mRS) score at six months post-stroke, which was categorized into two groups: mild to moderate disability (mRS 0-3) and severe disability (mRS 4-5). These two groups were compared using the Mann-Whitney U test for continuous variables and the Chi-square or Fisher's exact test for categorical variables, depending on the expected frequency distribution. A multivariate logistic regression analysis was performed to identify predictors of severe disability at six months. Variables that were significantly associated with severe disability in the univariate analysis ($p < 0.05$) were included in the multivariate model. The significance level for all statistical tests was set at $p < 0.05$.

3. Results

mRS at admission was 3 (2; 4) and at 6 months was 2 (0;3). The difference was highly statistically significant ($p<0.001$). Based on the values of mRS at 6 months we split the group into two groups: patients with mild/moderate disability (mRS 0-3) and patients with severe disability (mRS 4-5). There were statistically significant differences between the two groups regarding the age, presence of HF, NIHSS score, resistin levels, CRP and lesion volume.

Table 1. Comparison of group characteristics between patients with mild to moderate disability and patients with severe disability

Variables		Patients with mild to moderate disability (n=103)	Patients with severe disability (n=18)	p-value
Age (years)*		71 (65; 78.5)	76.5 (74.4; 80.2)	0.011
Sex	F	57 (55.3%)	11 (61.1%)	0.8
	B	46 (44.7%)	7 (38.9%)	
BMI (kg/m^2)*		27.7 (24.8; 31.2)	25.8 (22.5; 28.6)	0.29
Smoking	No	91 (88.3%)	16 (88.9%)	1
	Yes	12 (11.7%)	2 (11.1%)	
AH	No	16 (15.5%)	3 (16.7%)	1
	Yes	87 (84.5%)	15 (83.3%)	
AF	No	71 (58.9%)	14 (77.8%)	0.63
	Yes	32 (31.1%)	4 (22.2%)	
HF	No	95 (92.2%)	10 (55.6%)	<0.001

IHD	Yes	8 (7.8%)	8 (44.4%)	1
	No	80 (77.7%)	14 (77.8%)	
	Yes	23 (22.3%)	4 (22.2%)	
Valvulopathy	No	88 (85.4%)	14 (77.8%)	1
	Yes	15 (14.6%)	4 (22.2%)	
DM	No	71 (68.9%)	14 (77.8%)	0.63
	Yes	32 (31.1%)	4 (22.2%)	
Dyslipidemia	No	21 (20.4%)	5 (27.8%)	0.69
	Yes	82 (79.6%)	13 (72.2.%)	
NIHSS score		7 (4; 10.7)	12.5 (4.5; 15)	0.019
Leptin (ng/mL)*		50 (15.8; 91.1)	36.4 (5.9; 107.2)	0.68
Resistin (ng/mL)*		13.6 (9.1; 17.8)	21.6 (13.9; 24.4)	0.006
CRP (mg/L)*		1.7 (0.5; 4.9)	3.5 (0.5; 9)	<0.001
MCA stroke	No	58 (56.3%)	6 (33.3%)	0.12
	Yes	45 (43.7%)	12 (66.7.%)	
Lesion volume (mL)		14.9 (5.8; 29.5)	34.8 (10; 46.2)	0.019
Carotid plaque	No	20 (19.4%)	11 (33.3%)	0.52
	Yes	83 (80.6%)	16 (88.9%)	

A multivariate logistic regression was employed in order to find out which variables might be independently associated with severe disability at six months after an AIS. Only the presence of HF increased the chance of severe disability in an independent manner.

Table 2. Multivariate logistic regression for disability

Variables	B	P	OR	95% C.I.for OR	
				Min	Max
Age	0.040	0.15	1.041	0.985	1.101
Presence of HF	1.970	0.004	7.170	1.897	27.092
Lesion voluke	0.019	0.35	1.019	0.979	1.061
NIHSS score	0.083	0.164	1.087	0.967	1.222
Resistin	0.007	0.74	1.007	0.965	1.051
Constant	-5.514	0.011	0.004		

4. Discussion

The present study aimed to identify predictors of six-month outcomes in patients who suffered from AIS, using the mRS as a measure of disability. We explored the associations between demographic factors, clinical characteristics, laboratory markers, and neuroimaging findings with functional outcomes. The study's findings provide valuable insights into the factors that influence recovery after AIS, which can inform clinical practice and guide post-stroke care.

HF emerged as an independent predictor of severe disability at six months post-stroke, with patients having HF showing a significantly higher risk of poor outcomes. This finding highlights the complex interplay between cardiovascular health and stroke recovery. HF significantly impacts stroke outcomes by exacerbating both the initial injury and complicating the recovery process through several interconnected mechanisms. The reduced cerebral perfusion is caused by the decreased cardiac output characteristic of HF. This impaired blood flow limits the brain’s ability to receive adequate oxygen and nutrients, especially during an AIS, where the brain's demand for

oxygen is already compromised. The resulting hypoperfusion can lead to larger or more severe ischemic lesions, directly worsening neurological outcomes [35]. Additionally, HF is associated with chronic systemic inflammation, which can amplify the inflammatory response triggered by a stroke[36]. Elevated levels of proinflammatory cytokines, such as TNF-α and IL-6, in HF patients can exacerbate neuronal damage and impair the blood-brain barrier, leading to increased brain edema and secondary brain injury[37]. This inflammatory state worsens the acute damage and hinders the brain's ability to recover, reducing the effectiveness of neuroplasticity mechanisms critical for functional recovery post-stroke [38]. Neurohormonal activation, including the upregulation of the renin-angiotensin-aldosterone system and sympathetic nervous system, is another pathway through which HF could exacerbates stroke outcomes[39]. These systems induce vasoconstriction and promote fluid retention, further compromising cerebral perfusion and exacerbating ischemic injury. Moreover, neurohormonal activity can increase oxidative stress, leading to additional neuronal damage and impairing the recovery of the brain's functional networks[40]. The thromboembolic risk associated with HF, particularly in patients with concurrent AF, also plays a role in worsening stroke outcomes[41]. The blood stasis and clot formation in the heart increases the likelihood of embolic strokes, which can further complicate recovery by introducing additional ischemic events or enlarging existing infarcts. Moreover, the presence of HF may limit a patient's ability to participate in rehabilitation programs, further hindering recovery[42]. Patients with HF often have reduced exercise tolerance due to fatigue, dyspnea, and overall frailty, which limits their ability to participate fully in rehabilitation programs[43]. This reduced participation can significantly hamper recovery, as physical rehabilitation is crucial for regaining functional independence after a stroke[44]. Furthermore, HF patients are at increased risk for recurrent hospitalizations due to decompensation, which can interrupt or delay rehabilitation efforts and negatively affect the continuity of care. These frequent hospitalizations also expose patients to additional risks, such as hospital-acquired infections, which can further complicate recovery. These results suggest that stroke patients with HF require targeted interventions, possibly including optimized cardiac management and tailored rehabilitation strategies, to improve their functional outcomes. Integrating cardiovascular exercise into stroke rehabilitation programs can address the dual challenges of neurological and cardiovascular recovery. Studies have demonstrated that exercise-based cardiac rehabilitation not only improves cardiovascular outcomes but also supports neuroplasticity and cognitive recovery in stroke survivors[45,46]. Cardio-neuro rehabilitation programs should include tailored aerobic and resistance exercises that are safe for HF patients, with intensity levels adjusted according to the patient's cardiovascular capacity[47]. The exercise regimen in HF patients can be improved with cardiac implantable devices[48,49].

In our study age was associated with severe disability at six months after an AIS, in univariate analysis. Even if the association was not kept in the multivariate analysis, as the statistical threshold was slightly surpassed (p=0.1), the trend is clear. Older age was associated with a higher likelihood of severe disability (mRS 4-5) at six months, a result consistent with previous research[10]. Age is a well-known determinant of stroke recovery, as older patients often have less physiological reserve, more comorbid conditions, and a reduced capacity for neuroplasticity[50]. This finding underscores the importance of age-specific strategies in stroke management, where older patients may benefit from more aggressive rehabilitation and closer monitoring to optimize recovery[51].

The severity of the stroke at presentation, as measured by the NIHSS, was also a significant predictor of outcomes in univariate analysis, but again the statistical threshold was slightly surpassed in the multivariate analysis (p=0.1). Higher NIHSS scores at admission were associated with worse mRS scores at six months. Other studies

showed that NIHSS is widely recognized as a reliable indicator of stroke severity and a strong predictor of long-term functional outcomes[52]. The NIHSS score reflects the extent of neurological impairment, and its strong correlation with mRS underscores the importance of early and accurate assessment of stroke severity for prognostication and treatment planning[53].

Resistin, an adipokine associated with inflammation and insulin resistance, was also higher in patients with severe disability. However, its independent predictive value was not confirmed in the multivariate analysis. Resistin is involved in inflammatory pathways by stimulating the expression of proinflammatory cytokines such as TNF-α, IL-6, and IL-12 in macrophages and monocytes [54]. Additionally, it may contribute to the development of brain edema by disrupting the integrity of the endothelial layers of arteries[55]. Inflammation plays a dual role in stroke, contributing both to initial damage and to the healing process. These actions can exacerbate neurodamage and impair stroke recovery. The role of resistin in stroke outcomes remains unclear, with some studies suggesting a detrimental effect on recovery, while others have found no significant association[18,20,56]. A study by Ciancarelli et al. found that leptin, but not resistin, was predictive for neurorehabilitation[57]. Another study by Carbone et al. found that a ratio of adipokines predicted neurological recovery at day 90 [58]. The variability in resistin's impact on stroke outcomes might be explained by its interaction with other inflammatory markers and pathways, which could either amplify or reduce its effects depending on the individual patient's condition. Additionally, genetic and environmental factors, as well as comorbid conditions like diabetes or obesity, may influence resistin levels and their effects, further complicating the interpretation of results. The inconsistent findings across studies may be due to differences in study populations, measurement methods, and the timing of biomarker assessment. Further research is needed to clarify the role of resistin and other adipokines in stroke prognosis.

Neuroimaging findings, particularly the volume of the ischemic lesion, were also significant predictors of functional outcomes. Larger lesion volumes were associated with higher mRS scores, indicating greater disability. This result is consistent with previous studies demonstrating a strong correlation between lesion size and stroke severity [27,59]. Lesion volume is a direct measure of the extent of brain damage, and its relationship with functional outcomes underscores the importance of advanced imaging techniques in the early assessment of stroke patients[60]. Integrating imaging data into predictive models could enhance the accuracy of outcome predictions and guide therapeutic decisions.

Future studies should focus on developing and validating integrated rehabilitation protocols that specifically address neurological recovery, taking into account the predictive variables identified in this study and other, to improve functional outcomes and reduce long-term disability in stroke patients. The identification of HF as an independent predictor of severe disability might indicate the necessity for personalized rehabilitation strategies. For patients with HF, the rehabilitation program should not only focus on standard post-stroke neurological recovery but also include targeted cardiovascular interventions. These patients could benefit from a multidisciplinary approach integrating cardiologists, neurologists, and physical therapists to develop a comprehensive care plan. This might include: regular checkups at the cardiologist (clinical examination, echocardiograms and monitoring for arrhythmias); specialized exercise programs designed to improve both cardiovascular function and neurological outcomes (for example: graded aerobic exercises tailored to the patient’s cardiac tolerance can help improve overall stamina and support neurological recovery); increase communication between cardiologists and neurologists to ensuring that the management of HF is in accordance with neurorehabilitation goals, in order to reduce

the probability of rehospitalization and improve functional outcomes. The association between age, NIHSS score, and long-term disability suggests that older patients and those with more severe initial strokes require closer monitoring and more proactive follow-up care. Regular assessments using the mRS and other functional measures could help in early identification of patients at risk of poor outcomes, allowing for timely interventions that could improve recovery trajectories. Elevated levels of biomarkers after an AIS that predict a worse outcome could be pivotal in identifying patients who would benefit from a more aggressive anti-inflammatory management approach. By targeting these high-risk patients with specific anti-inflammatory therapies early in the recovery process, clinicians could potentially decrease the extent of neurological damage and improve overall functional outcomes.Despite the valuable insights gained from this study, several limitations need to be acknowledged. The relatively small sample and the single-center design may limit the generalizability of the findings to broader populations, particularly those with different demographic and clinical characteristics, asthe patient population in this study may differ in terms of demographics, comorbidities, and stroke care practices from those in other regions or countries. The applicability of our findings to broader, more diverse populations remains uncertain. The sample size of 121 patients reduces the study's statistical power, increasing the risk of type II errors and some associations may not be detected. This limitation is particularly important when considering the multivariate analysis, where the number of variables included in the model may lead to overfitting. The result should also be perceived with caution due to the specific circumstances of the study, the COVID-19 pandemic. The study faced a significant loss to follow-up, with 56% of patients withdrawing or not attending the six-month follow-up, primarily due to COVID-19 concerns. The exclusion of a significant number of patients due to loss to follow-up, primarily because of COVID-19-related concerns, may have introduced selection bias. Our final cohort might not fully represent the considerable large population of AIS patients. Those who were lost to follow-up could have different outcomes compared to those who completed the study, potentially skewing the results. Additionally, patients who withdrew from the study due to fear of contracting COVID-19 or other factors might have had distinct clinical profiles, leading to a non-random sample that could bias the findings. Furthermore, the study's cross-sectional assessment of inflammatory biomarkers, such as CRP and resistin, limits the ability to understand their dynamic changes over time and their impact on long-term outcomes.

5. Conclusions

This study provides valuable insights into the factors that predict six-month outcomes in patients with AIS, particularly highlighting the roles of age, stroke severity, heart failure, inflammatory markers, and lesion volume in influencing long-term disability as measured by the mRS. Our findings suggest that these variables are significant predictors of recovery, and they underscore the importance of a comprehensive approach to patient assessment and management early in the course of stroke treatment. Future research should aim to validate these findings in larger, more diverse populations and explore the potential benefits of targeted interventions based on the identified risk factors.

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