MEDICAL UNIVERSITY "Prof. Dr. Paraskev Stoyanov" – Varna

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Predictive Factors for Mortality in Young and Middle-Aged Patients with Ischemic Stroke

Summary of the Doctoral Dissertation for the Award of the Degree of Doctor of Philosophy (PhD)

Scientific Supervisor: Assoc. Prof. Darina Kirilova Georgieva-Hristova, MD, PhD

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The dissertation comprises 195 pages and includes 46 figures and 41 tables. The bibliography contains a total of 256 references, 4 in Cyrillic script and 252 in Latin script. The dissertation has been discussed and recommended for defence by the Department of Neurology and Neurosciences, Medical University “Prof. Dr. Paraskev Stoyanov” – Varna.

All studies included in the dissertation were conducted at:

Department of Neurology and Neurosciences, Medical University “Prof. Dr. Paraskev Stoyanov” – Varna;

Second Clinic of Neurology with intensive care Unit (ICU) and Stroke unit, University hospital “St.Marina”, Varna

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ABBREVIATIONS

AF	Atrial fibrillation
ASPECTS	Alberta Stroke Program Early CT Score
CLHF	Chronic left-sided heart failure
CRP	C-reactive protein
DM	Diabetes mellitus
DVT	Deep vein thrombosis
GCS	Glasgow Coma Scale
HR	Heart rate
HS	Haemorrhagic stroke
HTN	Arterial hypertension
IHD	Ischaemic heart disease
IS	Ischaemic stroke
MCA	Middle cerebral artery
MI	Myocardial infarction
NCPHA	National Centre for Public Health and Analyses
NIHSS	National Institutes of Health Stroke Scale
OSA	Obstructive sleep apnoea
PCA	Posterior cerebral artery

PFO Patent foramen ovale

R–L shunt Right-to-left shunt

SBP Systolic blood pressure

SITS Safe Implementation of Treatments in Stroke

TIA Transient ischaemic attack

TOAST Trial of ORG 10172 in Acute Stroke Treatment

WHO World Health Organization

I. INTRODUCTION

Ischaemic stroke (IS) remains a leading cause of mortality and disability worldwide, despite advances in prevention and treatment. According to the World Health Organization (WHO), it is the second most common cause of death in people over 60 years and the fifth among individuals aged 15–59 years. In Bulgaria, data from the National Centre for Public Health and Analyses (NCPHA) indicate that more than 45,000 new cases of IS are diagnosed annually, of which approximately 3,500–3,600 occur in individuals under 55 years of age. This underscores the substantial burden of the disease among young and middle-aged patients and necessitates a focus on the specific factors that determine an unfavourable outcome.

Young patients often have a different aetiology, risk profile, and fewer comorbidities compared with older individuals. This renders prognostic assessment in this population both challenging and clinically significant.

Identifying predictive factors for mortality in young and middle-aged patients with IS is essential for optimising therapeutic strategies, improving communication with patients and their families, and ensuring efficient resource management during the acute post-stroke period.

A more precise prognostic approach in young and middle-aged patients with IS has the potential to improve survival and reduce long-term social and economic consequences. This can be achieved through more targeted and effective treatment, as well as more appropriate allocation of healthcare resources.

II. AIM AND OBJECTIVES

1. Aim

The aim of the present dissertation is to conduct a retrospective, observational, single-center cohort study in patients aged up to 59 years with acute ischemic stroke, with the purpose of identifying independent predictors of in-hospital mortality through the assessment of the influence of risk factors, demographic characteristics, clinical status at admission, laboratory and neuroimaging findings, duration of hospitalization, and treatment approaches.

2. Objectives

In order to achieve this aim, the following specific objectives were set:

2.1. To perform a retrospective cohort analysis of patients aged 18–59 years with acute ischemic stroke, hospitalized at the Second Clinic of Neurology, St. Marina University Hospital – Varna, during the period 2017–2022.

2.2. To describe the clinical, demographic, and imaging characteristics of patients with ischemic stroke aged up to 59 years.

2.3. To analyze the relationship between comorbidities and the likelihood of a fatal outcome during the acute phase of ischemic stroke in patients aged 18–59 years.

2.4. To evaluate the impact of clinical status at admission (including NIHSS score, vital parameters, and presence of consciousness disturbances) on the risk of in-hospital mortality among patients aged 18–59 years.

2.5. To investigate the role of neuroimaging findings, including lesion localization, hemispheric involvement, presence of a hyperdense cerebral artery sign, and ASPECTS score—in predicting mortality in patients aged 18–59 years.

2.6. To assess the prognostic significance of laboratory parameters (including inflammatory and metabolic markers) and length of hospital stay as potential predictors of mortality in patients aged 18–59 years.

2.7. To analyze the association between etiological subtypes of ischemic stroke, classified according to the TOAST criteria, and mortality among patients aged 18–59 years.

2.8. To apply multivariate logistic regression analysis to determine independent risk factors associated with in-hospital mortality in patients aged 18–59 years.

III. MATERIALS AND METHODS

3.1 Materials

3.1.1 Clinical material

The clinical material in the present study comprises a total of 168 patients with ischemic stroke, hospitalized at the Second Clinic of Neurology of St. Marina University Hospital – Varna, during the period from 2017 to 2022. The patients were treated at the Second Clinic of Neurology with ICU and Stroke unit. The study sample was stratified into two groups: a target group consisting of 67 patients who experienced a fatal outcome during hospitalization, and a control group including 101 patients. All participants were aged between 18 and 59 years.

3.1.2 Inclusion and exclusion criteria for the target and control groups

Inclusion criteria:

Patients with confirmed acute ischaemic stroke, hospitalised at the Second Clinic of Neurology with the Intensive Care Unit for Neurological Diseases and the Stroke Unit, UMHAT “St. Marina” EAD – Varna, in 2017–2022.

Age 18–59 years at the time of admission.

Clinical and imaging verification of acute ischaemic stroke.

Exclusion criteria:

Patients aged <18 or >59 years.

Patients diagnosed with intracerebral haemorrhage or subarachnoid haemorrhage.

Ethics approval
The study was approved by the Research Ethics Committee of the Medical University – Varna (Decision No. 133, 22 June 2023).

3.2 Methods

3.2.1 Clinical methods

A retrospective review of medical records of patients with ischaemic stroke was conducted. Sources included discharge summaries, hospital case histories, laboratory results, imaging studies, and standard 12-lead electrocardiogram (ECG) recordings.

3.2.2 Clinical assessment of vital signs at admission

Systolic blood pressure (SBP) and heart rate (HR) were measured upon patients' admission to the clinic in order to provide an objective assessment of their hemodynamic status at the time of hospitalization. The measurements were performed at rest, with the patient in a supine position, by qualified medical personnel. In the majority of cases, the parameters were automatically recorded using a multifunctional vital signs monitoring device, while in the remaining patients, they were obtained using a calibrated noninvasive blood pressure monitor. All measurements were taken within the first 30 minutes after hospital admission, prior to the initiation of specific treatment.

3.2.3 Determination of patients' risk profile

In all patients included in the study (both target and control groups), the presence of major risk factors for acute ischaemic stroke and stroke-related mortality was assessed. Risk factors were systematised as follows:

Non-modifiable: sex, age, prior ischaemic stroke or transient ischaemic attack (TIA), prior myocardial infarction (MI).

Modifiable: arterial hypertension (HTN), atrial fibrillation (AF), ischaemic heart disease (IHD), chronic left-sided heart failure (CHF), diabetes mellitus (DM), dyslipidaemia, obesity, smoking, alcohol misuse, and use of psychoactive substances.

Less frequently documented modifiable risk factors: right-to-left shunt (R–L shunt), acute inflammatory process, obstructive sleep apnoea (OSA), deep vein thrombosis (DVT), and malignant neoplasms.

3.2.4 Laboratory investigations

Laboratory testing was performed in the Clinical Laboratory of UMHAT "St. Marina" EAD – Varna.

Leukocyte count: automated haematology analysers Sysmex XN-1000 and ADVIA 2120.

Biochemical analysis (including serum C-reactive protein [CRP], sodium, and glucose): automated biochemical analyser ADVIA 1800+ (consolidated system).

3.2.5 Neuroimaging studies

Computed tomography (CT) of the head
Examinations were performed on Siemens [Somatom] Spirit and [Somatom] Definition CT scanners using a standard non-contrast head protocol.

Magnetic resonance imaging (MRI) of the head
Examinations were performed on a Siemens MAGNETOM Verio 3T MRI scanner.

3.2.6 Rating scales

3.2.6.1 National Institutes of Health Stroke Scale (NIHSS)

Neurological deficit at admission was assessed using the standardised NIHSS (National Institutes of Health Stroke Scale). According to the total score, stroke severity was classified as:

0 points: no neurological symptoms

1–4 points: mild neurological deficit

5–15 points: moderate neurological deficit

16–20 points: severe neurological deficit

>21 points: very severe neurological deficit

3.2.6.2 Glasgow Coma Scale (GCS)

Level of consciousness at admission was assessed using the Glasgow Coma Scale (GCS). The maximum total score is 15.

<8 points: unfavourable prognosis

≥8 points: more favourable prognosis

3.2.6.3 Alberta Stroke Program Early CT Score (ASPECTS)

Assessment of early ischaemic changes in the middle cerebral artery (MCA) territory was performed using the ASPECTS score on non-contrast CT at admission. ASPECTS is a quantitative scale for rating early ischaemic changes in the MCA territory on computed tomography. The maximum score is 10.

ASPECTS ≤7 - unfavourable prognosis

ASPECTS >7 - more favourable prognosis

3.2.7 Statistical methods for data analysis

Data processing was performed using IBM SPSS Statistics, version 20.0 for Windows. Normality of continuous variables was assessed by visual inspection of histograms and bar charts, as well as by evaluating skewness and kurtosis statistics. Owing to the lack of normal distribution in most continuous variables, between-group comparisons were conducted using the non-parametric Mann–Whitney U test.

For comparisons of proportions between categorical variables, the χ^2 test and Fisher's exact test were applied, depending on expected cell counts. Effect size was estimated using the odds ratio (OR) with a 95% confidence interval (CI).

The dependent variable, 'fatal outcome', was binary (1 = deceased, 0 = survived). Categorical independent variables were dichotomised according to clinical cut-offs and coded as 1 = present, 0 = absent. Under this coding, the OR quantifies the odds of a fatal outcome in the presence of the factor relative to its absence; thus, OR > 1 indicates a higher odds of fatal outcome, whereas OR < 1 indicates a lower odds (protective effect).

Given the limited number of events (67 in-hospital deaths) and to avoid overfitting, a multistep approach was adopted with the construction of four separate multivariable logistic models (Models A–D). Each model included a different group of predictors—clinical, laboratory, demographic, and integrated factors—selected based on significance in univariable analyses and clinical relevance. In developing the final composite model (Model D), inclusion of highly correlated variables was avoided to minimise multicollinearity.

Model adequacy was evaluated using: the Omnibus χ^2 test for overall model significance, the −2 Log Likelihood for model comparison, Nagelkerke R^2 as a measure of explained variance, the Hosmer–Lemeshow goodness-of-fit test, overall classification accuracy, as well as sensitivity and specificity. A p-value < 0.05 was considered statistically significant.

IV. Original Findings

Description of the Study Population

The present study included a total of 168 patients, allocated into two main groups. The target group comprised 67 patients aged 18–59 years who died during hospitalization as a consequence of ischemic stroke. The control group included 101 patients in the same age range (18–59 years) who survived the ischemic stroke.

Demographic Data

In the target group, the mean age was 51.99 years.

In the control group, the mean age was 47.52 years.

In the target group (n = 67), 51 (76.1%) were men and 16 (23.9%) were women.

In the control group (n = 101), men accounted for 70.3% (n = 71) and women for 29.7% (n = 30).

1.2 Non-modifiable risk factors and their association with lethal outcome in Ischemic stroke

The mean age in the target group was significantly higher (51.99 years) than in the control group (47.52 years), with the difference reaching statistical significance ($p < 0.001$). This underscores the role of older age as an adverse prognostic factor among patients aged ≤59 years with ischemic stroke.

No statistically significant association was found between sex and lethal outcome ($\chi^2 = 0.687$, df = 1, $p = 0.407$). This indicates that sex was not a statistically significant predictor of mortality in patients aged ≤59 years with ischemic stroke in the present study. The proportions of men and women did not differ significantly between the deceased and surviving groups.

Regarding prior stroke, patients in the target group more frequently had a history of previous stroke (46.3% ischemic stroke and 4.5% hemorrhagic stroke) compared with the control group (17.0% ischemic stroke and 0% hemorrhagic stroke) (Figure 1), and this difference was statistically significant ($p < 0.001$). This suggests a strong association between a history of prior stroke and an unfavorable outcome following a subsequent event.

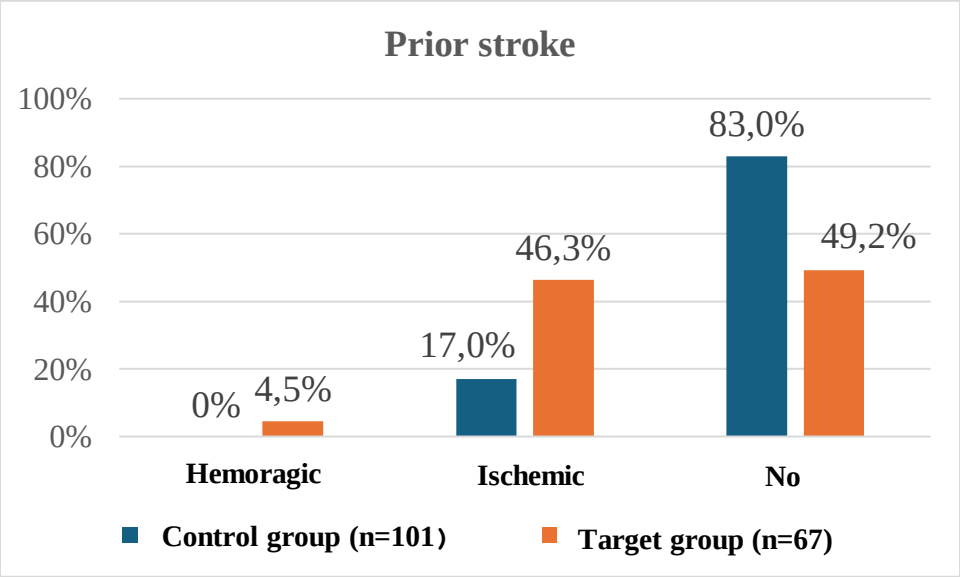

Figure 1. *Bar chart illustrating the frequency of prior stroke in the control and target groups.*

A prior transient ischemic attack (TIA) was identified in a small proportion of patients in the control group (5.0%), whereas no such cases were observed in the target group. As the difference

did not reach statistical significance ($p > 0.05$), no conclusions can be drawn regarding the prognostic value of TIA.

A prior myocardial infarction (MI) was more common among deceased patients - 30 (44.8%) compared with 15 (14.9%) in the control group (Figure 3). The difference was statistically significant ($p < 0.001$). A prior MI was associated with an odds ratio of 4.649 (95% CI: 2.241–9.645, $p < 0.001$).

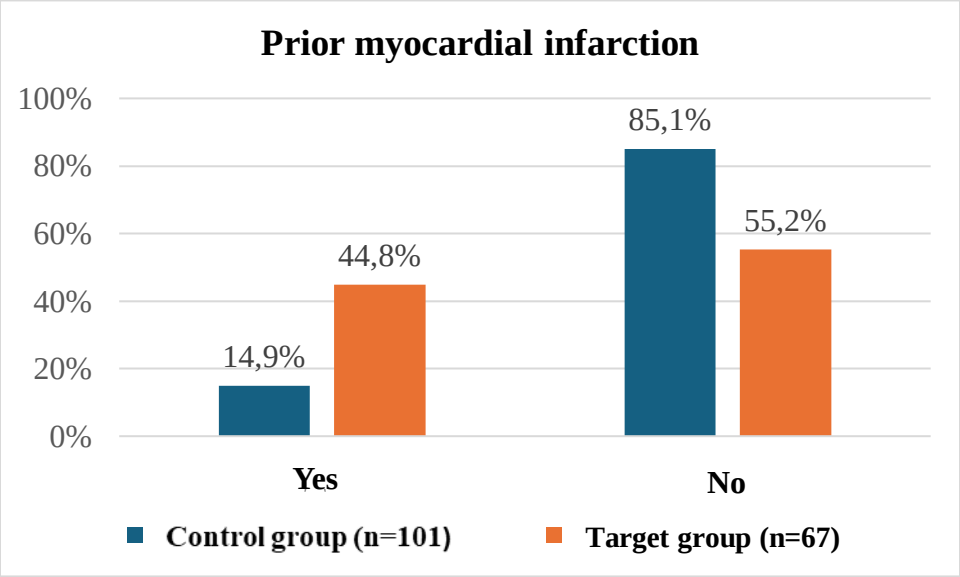

Figure 3. Bar chart illustrating the frequency of prior myocardial infarction in the control and target groups.

Table 1. *Distribution of non-modifiable risk factors by ischemic stroke outcome and statistical significance of the differences.*

Risk factor	**Category**	**Target group (n = 67), N (%)**	**Control group (n = 101), N (%)**	**p-value**
Age	N/A	51,99 ± 7,20 (*)	47,52 ± 8,11 (*)	< 0,001 (1)
	N/A			

Sex	Male	51 (76,1 %)	71 (70,3 %)	= 0,407 [(a)]
	Female	16 (23,9 %)	30 (29,7 %)	
Prior stroke	No	36 (49,2 %)	84 (83,0%)	<0,001 [(a)]
	IS	31 (46,3 %)	17 (17,0 %)	
	HS	3 (4,5 %)	0 (0,0 %)	
Prior MI	Yes	30 (44,8 %)	15 (14,4 %)	<0,001[(a)]
	No	37 (55,2 %)	86 (85.1 %)	

[(*)] Age values are presented as mean ± standard deviation.

[(1)] Result obtained using the Mann–Whitney U test: U = 2027.5, Z = –4.401, p < 0.001.

[(a)] Analysis performed using the χ^2 test.

[(b)] Analysis performed using Fisher's exact test.

2.Modifiable risk factors and lethal outcome in patients with ischemic stroke aged ≤59 years

2.1 Cardiovascular modifiable risk factors and their prognostic role for lethal outcome in ischemic stroke

Chronic left-sided heart failure was present in 57 (85.1%) of patients with a lethal outcome, compared with 34 (33.7%) in the control group (Figure 2). The difference was statistically significant ($p < 0.001$).

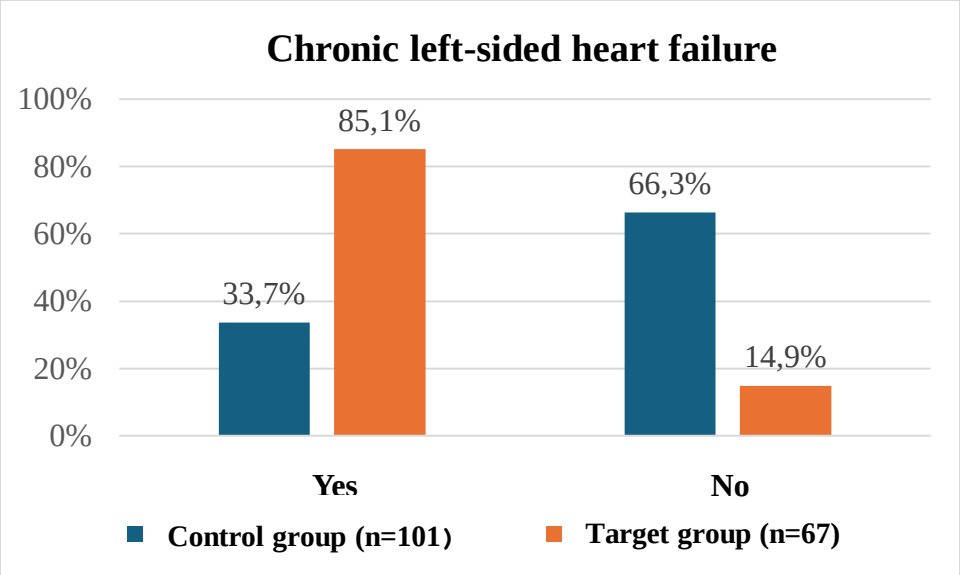

Figure 2. *Bar chart illustrating the frequency of chronic left-sided heart failure in the control and target groups.*

Ischemic heart disease (IHD) was documented in 24 (35.8%) of deceased patients, whereas among survivors it was observed in 7 (6.9%) patients (Figure 4). The difference was statistically significant ($p < 0.001$).

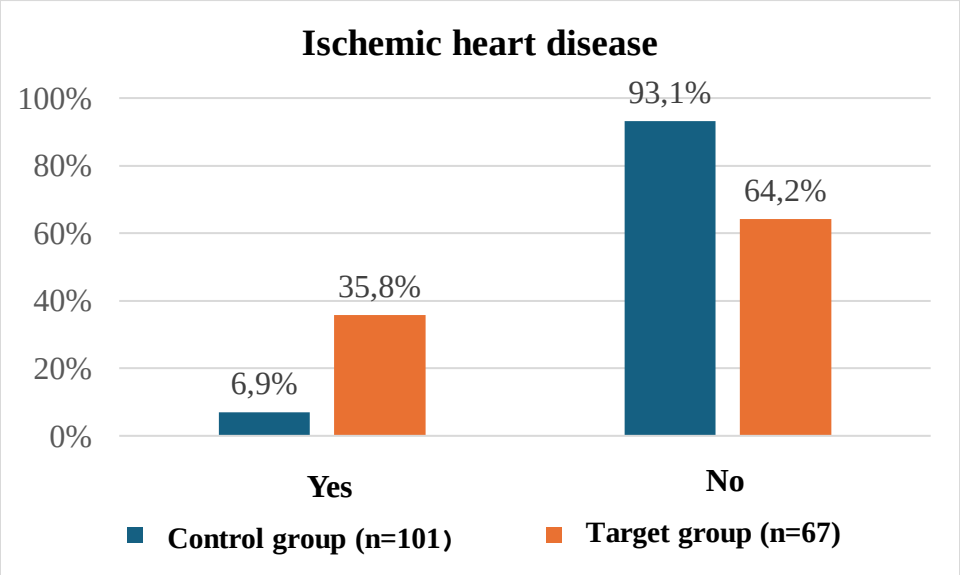

Figure 4. *Bar chart illustrating the frequency of ischemic heart disease in the control and target groups.*

Atrial fibrillation (AF) was identified in 6 (9.0%) of the deceased and in 2 (2.0%) of the survivors. Despite the higher frequency in the target group, the difference did not reach statistical significance ($p > 0.05$).

Hypertensive disease was similarly prevalent in both groups - 88.1% among the deceased and 90.1% in the control group with no statistically significant difference ($p = 0.676$).

Table 2. *Distribution of modifiable cardiovascular risk factors by ischemic stroke outcome and statistical significance of the differences.*

Risk factor	Category	Target group (n=67) N (%)	Control group (n=101) N (%)	p–value
HTN	Yes	59 (88,1 %)	91 (90,1 %)	0,676
	No	8 (11,9 %)	10 (9,9 %)	
AF	Yes	6 (9,0 %)	2 (2,0 %)	> 0,05
	No	61 (91,0 %)	99 (98,0 %)	
IHD	Yes	24 (35,8 %)	7 (6,9 %)	<0,001
	No	43 (64,2 %)	94 (93,1 %)	
CLHF	Yes	57 (85,1 %)	34 (33,7 %)	<0,001
	No	10 (14,9 %)	67 (66,3 %)	

2.1.1 Univariate Logistic Analysis of Odds Ratios (OR) for Lethal Outcome Associated with Cardiovascular Risk Factors

To further evaluate the prognostic impact of modifiable cardiovascular risk factors on mortality, univariate logistic regression analyses were conducted for each factor.
The strongest prognostic effect was observed for chronic left-sided heart failure (CLHF): patients with CLHF had more than elevenfold higher odds of death compared with those without CLHF (OR = 11.23, 95% CI: 5.10–25.00, $p < 0.001$). A pronounced effect was also found for ischemic heart disease (IHD), with an odds ratio of 7.495 (95% CI: 2.999–18.732, $p < 0.001$), indicating that patients with IHD had more than sevenfold higher odds of death compared with those without concomitant IHD. For hypertensive disease, the odds ratio was 0.810 (95% CI: 0.302–2.172), a result that did not reach statistical significance ($p > 0.05$). Regarding atrial fibrillation (AF), increased odds of death were noted (OR = 4.869, 95% CI: 0.952–24.895), but the result was not statistically significant ($p > 0.05$). This potential trend toward elevated risk is likely attributable to the small number of cases and the wide confidence interval (Table 3).

Table 3. *Univariate odds ratio estimates for cardiovascular risk factors.*

Risk factor	OR	95 % CI	p-value
HTN	0,810	0,302–2,172	> 0,05
AF	4,869	0,952 -24,895	> 0,05
IHD	7,495	2,999 – 18,732	< 0,001
CLHF	11,23	5,10–25,00	<0,001

2.2 Metabolic Modifiable Risk Factors and Their Prognostic Role for Lethal Outcome in Ischemic Stroke

In evaluating metabolic risk factors associated with outcomes of ischemic stroke in young and middle-aged patients, substantial differences were observed between the two study groups. Diabetes mellitus (DM) was more frequent in the target group - 22 of 67 patients (32.8%) - compared with the control group, where it was recorded in 16 of 101 patients (15.8%) (Figure 5). The difference was statistically significant ($p = 0.014$), which may be considered a potential predictor of lethal outcome following ischemic stroke in this age population.

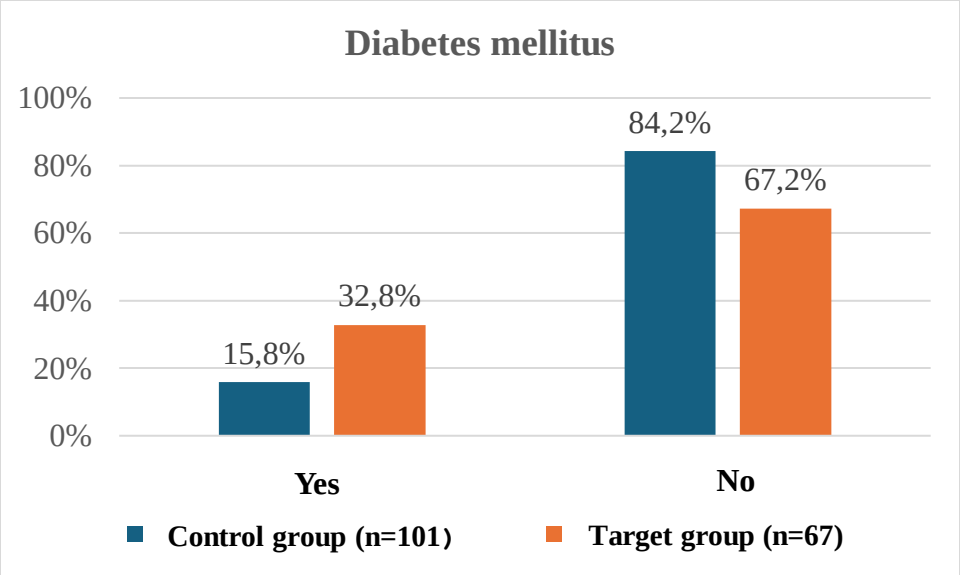

Figure 5. *Bar chart illustrating the frequency of diabetes mellitus in the control and target groups.*

Dyslipidemia also showed a statistically significant difference between the groups (p = 0.010). It was identified in 40 (59.7%) of patients in the target group and in 79 (78.2%) of controls (Figure 6).

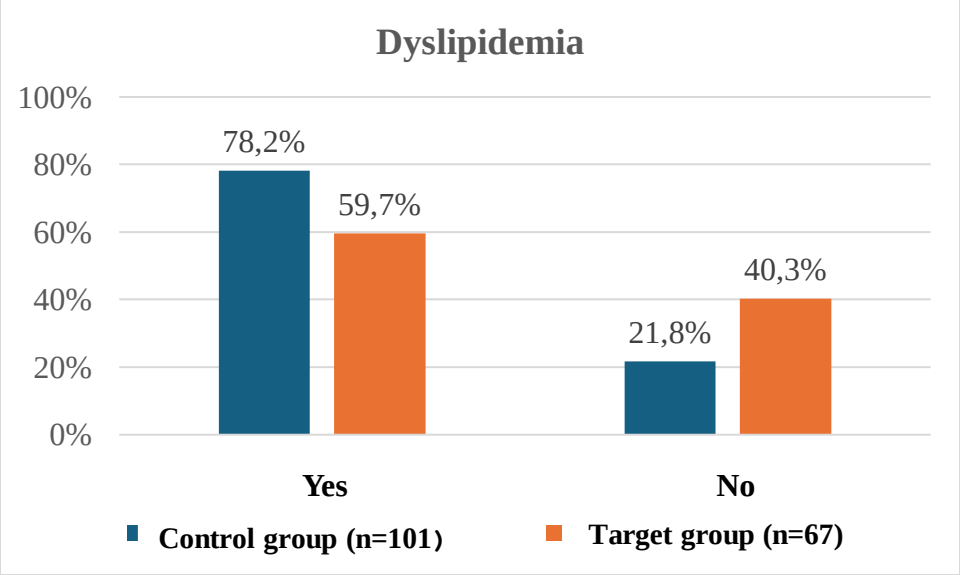

Figure 6. *Bar chart illustrating the frequency of dyslipidemia in the control and target groups.*

Regarding obesity, no substantial difference was observed between the groups - 9.0% in the target group versus 4.0% in the control group. The lack of statistical significance (p = 0.199)

does not allow obesity to be interpreted as a prognostic factor within the present analysis.

Table 4. *Distribution of modifiable metabolic risk factors by ischemic stroke outcome and statistical significance of the differences*

Risk factor	**Category**	**Target group (n=67) N (%)**	**Control group (n=101) N (%)**	**p-value**
DM	Yes	22 (32,8 %)	16 (15,8 %)	0,014 (b)
	No	45 (67,2 %)	85 (84,2 %	
Dyslipidemia	Yes	40 (59,7 %)	79 (78,2 %)	0,010 (a)
	No	27 (40,3 %)	22 (21,8 %)	
Obesity	Yes	6 (9,0 %)	4 (4,0 %)	0,199 (b)
	No	61 (91,0 %)	97 (96,0 %)	

[(a)] Analysis performed using the χ^2 test; [(b)] Analysis performed using Fisher's exact test.

2.2.1 Univariate Logistic Analysis of Odds Ratios (OR) for Lethal Outcome from Ischemic Stroke Associated with Metabolic Risk Factors

The univariate logistic regression analysis for metabolic risk factors provides additional insight into their prognostic influence on mortality.

For diabetes mellitus (DM), OR = 2.424 (95% CI: 1.229–4.781), reaching statistical significance ($p < 0.05$). This indicates that individuals with DM had 2.424-fold higher odds of death compared with those without DM.

For dyslipidemia, the univariate analysis showed OR = 0.385 (95% CI: 0.184–0.806), which was statistically significant ($p < 0.05$). This finding suggests a protective association of dyslipidemia with lethal outcome in the present cohort.

Regarding obesity, although an elevated OR = 2.385 was observed, the confidence interval (95% CI: 0.647–8.797) indicates a non-significant result ($p > 0.05$).

Table 5. *Univariate odds ratio estimates for metabolic risk factors.*

Risc factor	OR	95 % CI	p-value
DM	2,424	1,229 – 4,781	< 0,05
Dyslipidemia	0,385	0,184 – 0,806	< 0,05
Obesity	2,385	0,647 – 8,797	> 0,05

2.3 Behavioral Risk Factors and Their Prognostic Role for Lethal Outcome in Ischemic Stroke

The analysis of behavioral risk factors - smoking, alcohol abuse, and use of psychoactive substances did not reveal statistically significant differences between the target and control groups, nor an association with increased odds of lethal outcome among patients aged ≤59 years with ischemic stroke ($p > 0.05$) (Table 6).

Table 6*. Distribution of behavioral risk factors by ischemic stroke outcome and statistical significance of the differences.*

Risk factor	Category	Target group (n=67) N (%)	Control group (n=101) N (%)	p-value
Smoking	Yes	36 (53,7 %	60 (59,4 %)	0,467 [(a)]
	No	31 (46,3 %)	41 (40,6 %)	
Alcohol abuse	Yes	7 (10,4 %)	11 (10,9 %)	1,000 [(b)]
	No	60 (89,6 %)	90 (89,1 %)	
	Yes	4 (6,0 %)	8 (7,9 %)	

Use of psychoactive substances	No	(94,0 %)	(92,1 %)	0,765 (b)

(a) Analysis performed using the χ^2 test; (b) Analysis performed using Fisher's exact test.

3.Rarely Documented Modifiable Risk Factors and Their Prognostic Role for Lethal Outcome in Ischemic Stroke

The analysis of less frequently documented modifiable risk factors revealed the strongest statistical association between the presence of an acute inflammatory process and lethal outcome among patients with ischemic stroke. Acute inflammatory processes were recorded in 34.3% (n = 23) of deceased patients, compared with 7.9% (n = 8) of the control group (Figure 7), a difference that was statistically significant ($p < 0.001$) (Table 7). This underscores the potential prognostic value of systemic inflammation as an adverse factor in ischemic stroke among young and middle-aged patients.

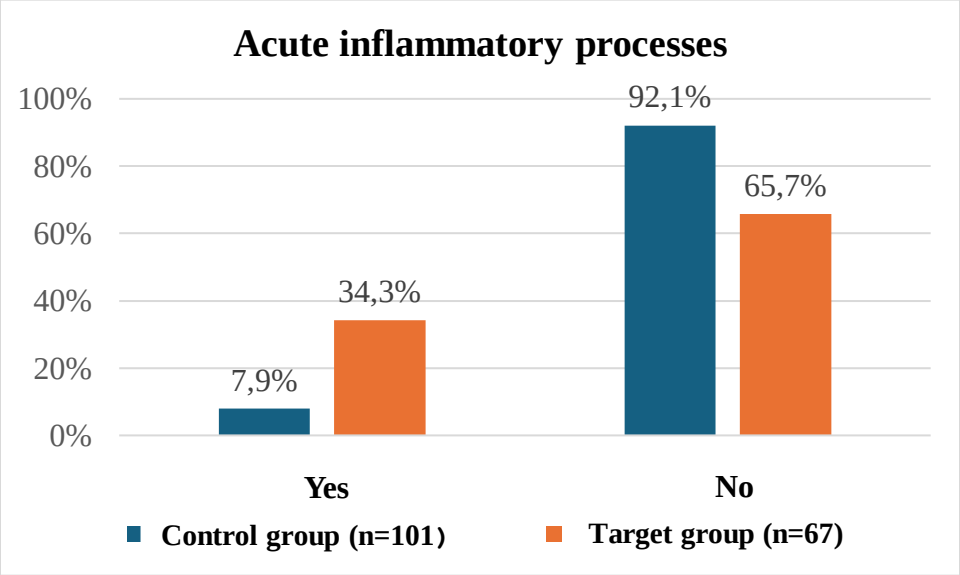

Figure 7. *Bar chart illustrating the frequency of acute inflammatory processes in the control and target groups.*

A p-value at the threshold of statistical significance was observed for deep vein thrombosis ($p = 0.050$), suggesting a possible association with increased mortality risk, though confirmation in larger cohorts is warranted.

Regarding the right-to-left (R–L) shunt - despite the statistical significance (p=0.002), the absence of cases in the target group and the low frequency of the shunt limit the ability to draw definitive conclusions.

Malignancy and obstructive sleep apnea did not show a statistically significant association with lethal outcome within the present study (p > 0.05), despite observed differences in frequency between the groups (Table 7).

Table 7. *Distribution of rarely documented modifiable risk factors by ischemic stroke outcome and statistical significance of the differences*

Risk factor	**Category**	**Target group (n=67) N (%)**	**Control group (n=101) N (%)**	**p -value**
R-L shunt	Yes	0 (0,0 %)	12 (11,9 %)	0,002 [(b)]
	No	67 (100 %)	89 (88,1 %)	
Acute inflammatory processes	Yes	23 (34,3 %)	8 (7,9 %)	<0,001[(a)]
	No	44 (65,7 %)	93 (92,1 %)	
Obstructive sleep apnea	Yes	2 (3,0 %)	0 (0,0 %)	0,158 [(b)]
	No	65 (97,0 %)	101 (100 %	
Deep vein thrombosis	Yes	10 (14,9 %)	5 (5,0 %)	0,050 [(b)]
	No	57 (85,1 %)	96 (95,0 %)	
Malignancy	Yes	7 (10.4 %)	5 (5.0 %)	0.224 [(b)]
	No	60 (89.6 %)	96 (95.0 %)	

[(a)] Analysis performed using the χ^2 test; [(b)] Analysis performed using Fisher's exact test.

3.1 Univariate Logistic Analysis of Odds Ratios (OR) for Lethal Outcome Associated with Rarely Documented Modifiable Risk Factors

The presence of an acute inflammatory process at admission emerged as the strongest predictor of lethal outcome in the univariate analysis. The estimated odds ratio (OR = 6.077; 95% CI: 2.518–14.662; $p < 0.001$) indicates that patients with a concomitant infection had more than sixfold higher odds of death compared with those without infection. A further significant association was observed for deep vein thrombosis (DVT), with OR = 3.368 (95% CI: 1.096–10.349; $p < 0.05$), reflecting a more than threefold increase in the odds of death in the presence of DVT.

The indicator regarding the right-to-left shunt is reported descriptively, without interpreting the direction of the effect, due to a discrepancy between the observed frequencies and the calculated OR/CI in the context of a small sample size and a zero cell.

Other factors – malignancy and obstructive sleep apnea did not show statistically significant associations with lethal outcome ($p > 0.05$) (Table 8).

Table 8. *Univariate odds ratio estimates for rarely documented modifiable risk factors.*

Risk factor	OR	95 % CI	p-value
R-L shunt	1,135	1,056 – 1,219	< 0,01
Acute inflammatory processes	6,077	2,518 – 14,662	< 0,001
Obstructive sleep apnea	0,970	0,930 – 1,012	> 0,05
Deep vein trombosis	3,368	1,096 – 10,349	< 0,05
Malignancy	2,240	0,680 – 7,379	> 0,05

4. Distribution and Comparative Analysis of the Number of Comorbidities in Patients with Ischemic Stroke

The analysis of comorbidity counts showed that the mean number in the target group (patients with a lethal outcome) was significantly higher (Mean = 4.28) than in the control group (Mean =

2.78), indicating an accumulation of multimorbidity among the deceased patients (Figures 8 and 9).

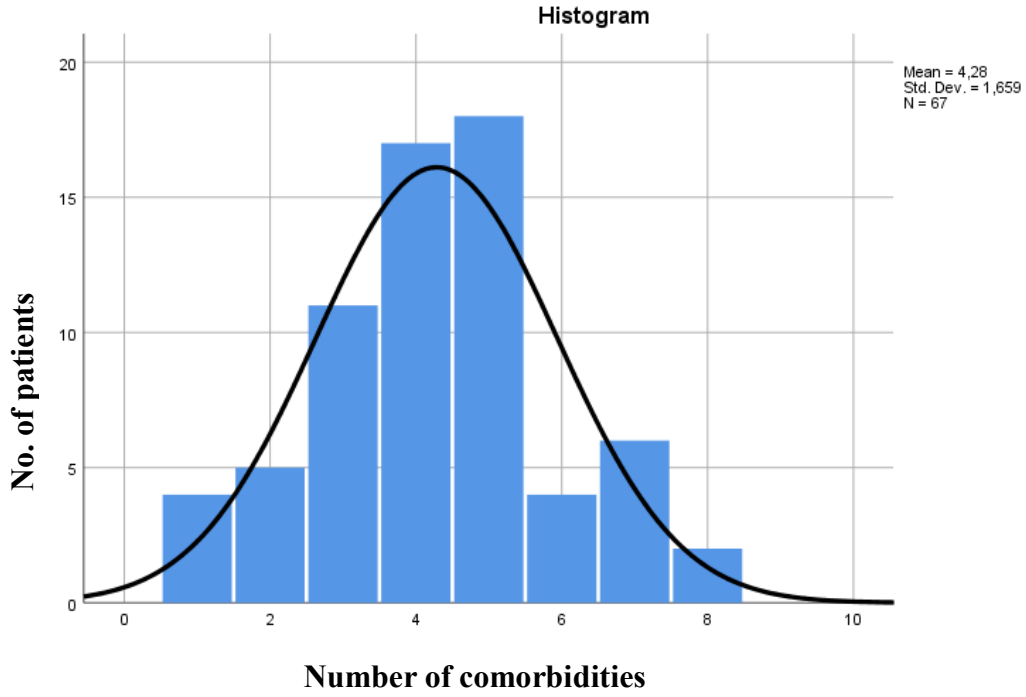

Figure 8. *Histogram of the number of comorbidities in the target group (n = 67).*

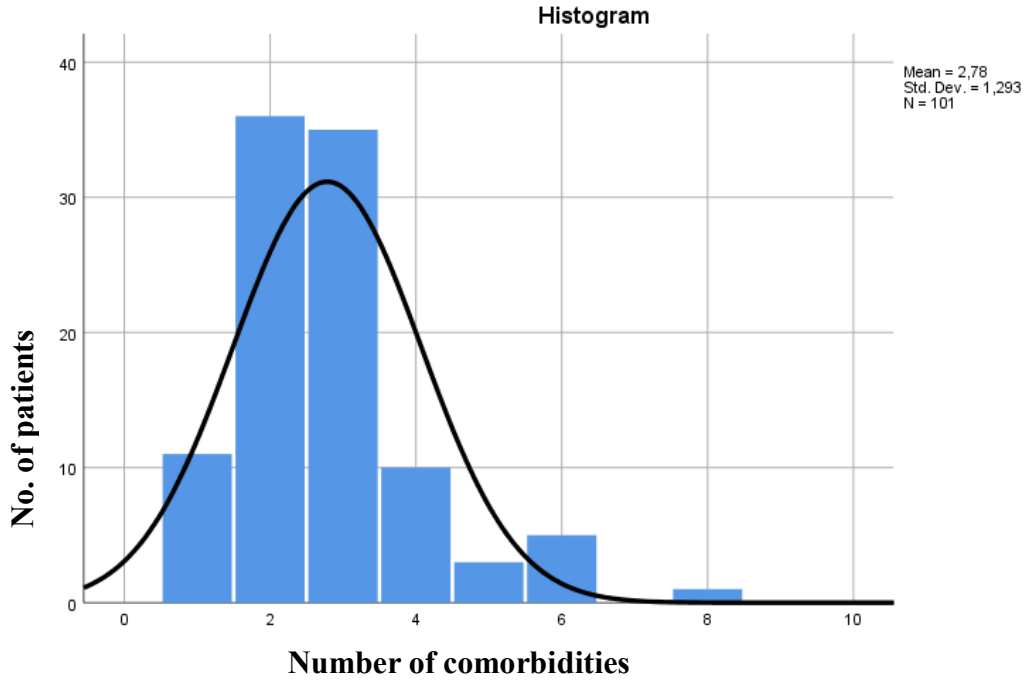

Figure 9. *Histogram of the number of comorbidities in the control group (n = 101).*

In the descriptive analysis of the number of comorbidities, clear differences in distribution were observed between the two study groups. In the target group, a higher proportion of patients had multiple comorbidities (e.g., five comorbitidies were most common - 26.9%), with counts reaching up to eight conditions (3.0%). In contrast, the control group showed clustering at lower counts (two and three comorbidities were most common -35.6% and 34.7%, respectively), and patients with ≥5 conditions were relatively few (8.9% overall). These findings indicate that cases with a greater number of comorbidities predominated in the group with a lethal outcome (Figure 10).

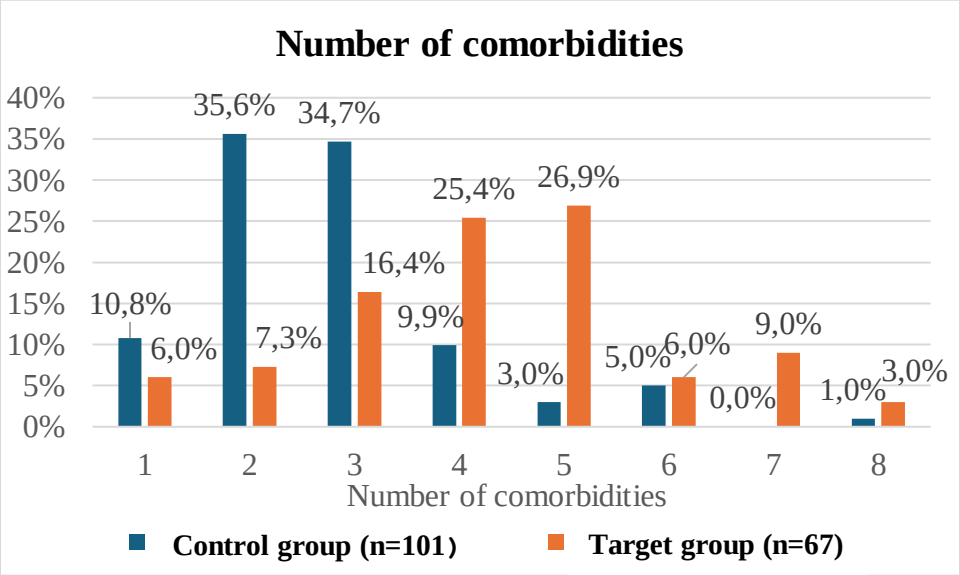

Figure 10*. Bar chart depicting the distribution and frequency of the number of comorbidities in the control and target groups.*

In the comparative analysis of the number of comorbidities between the deceased (target group) and survivors (control group), the Mann–Whitney U test was applied. The results demonstrated a statistically significant difference between the groups ($p < 0.001$). The mean rank in the target group (112.05) was markedly higher than in the control group (66.22), indicating a greater cumulative comorbidity burden among patients with a lethal outcome.

5. Etiological Subtypes According to the TOAST Classification and Their Prognostic Role for Lethal Outcome in Ischemic Stroke

The analysis of etiological subtypes based on the TOAST classification revealed that the largest proportion of patients in both groups were classified with large-artery atherosclerosis (91.0% in

the target group and 93.0% in the control group). A more pronounced difference was observed for the cardioembolism subtype, present in 9.0% of patients in the target group and only 2.0% in the control group. Lacunar infarction was observed exclusively in the control group (5.0%), with no such cases in the target group (Figure 11).

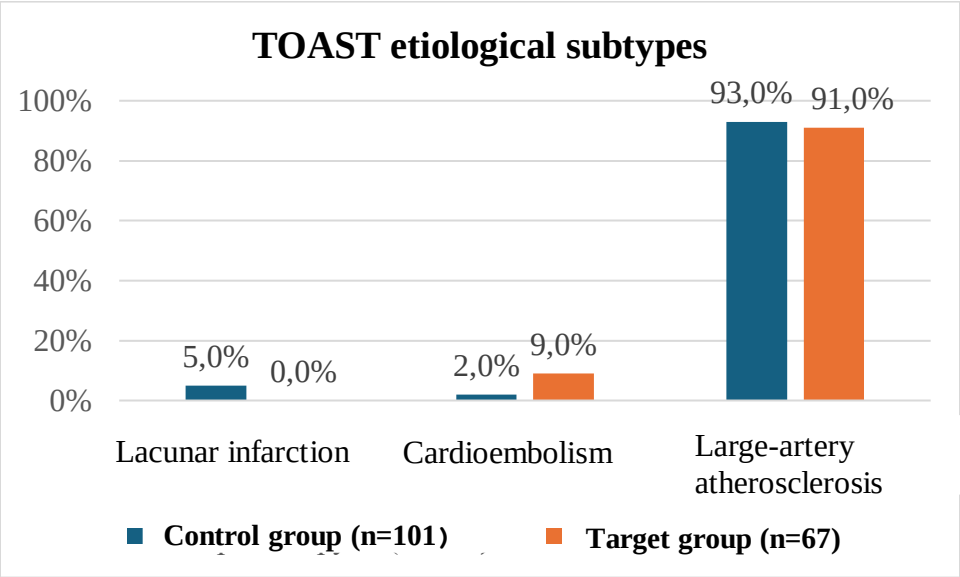

Figure 11. *Bar chart illustrating the distribution of TOAST etiological subtypes in the control and target groups.*

The analysis of the association between ischemic stroke etiological subtypes per the TOAST classification and mortality demonstrated a statistically significant relationship (p = 0.024). Despite this significance, interpretation should be cautious due to the small number of cases in two categories.

5.1 Univariate Logistic Analysis of Odds Ratios (OR) for Lethal Outcome by TOAST Classification

For the cardioembolic subtype, the estimated odds ratio (OR) was 4.87, indicating that, within the study sample, patients with this etiology had a higher frequency of lethal outcomes compared with the remaining subtypes. However, this result did not reach statistical significance (p = 0.060). It should therefore be interpreted with caution and considered a potential trend requiring confirmation in a larger cohort.
Other subtypes, including large-artery atherosclerosis, did not show a statistically significant association with lethal outcome.

Table 9. *Univariate odds ratios for lethal outcome by TOAST etiological subtypes.*

TOAST etiological subtype	OR	95 % CI	p-value
Large-artery atherosclerosis	0,76	0,24 – 2,36	0,770
Cardioembolic subtype	4,87	0,95 – 24,89	0,060

6.Assessment of neurological deficit using the NIHSS at admission as a predictor of mortality in patients with acute ischemic stroke

The mean NIHSS score in the control group was 7.00 (SD = 5.219), with most patients exhibiting lower scores on the scale (mode = 2; range, 1–20) (Figure 12).

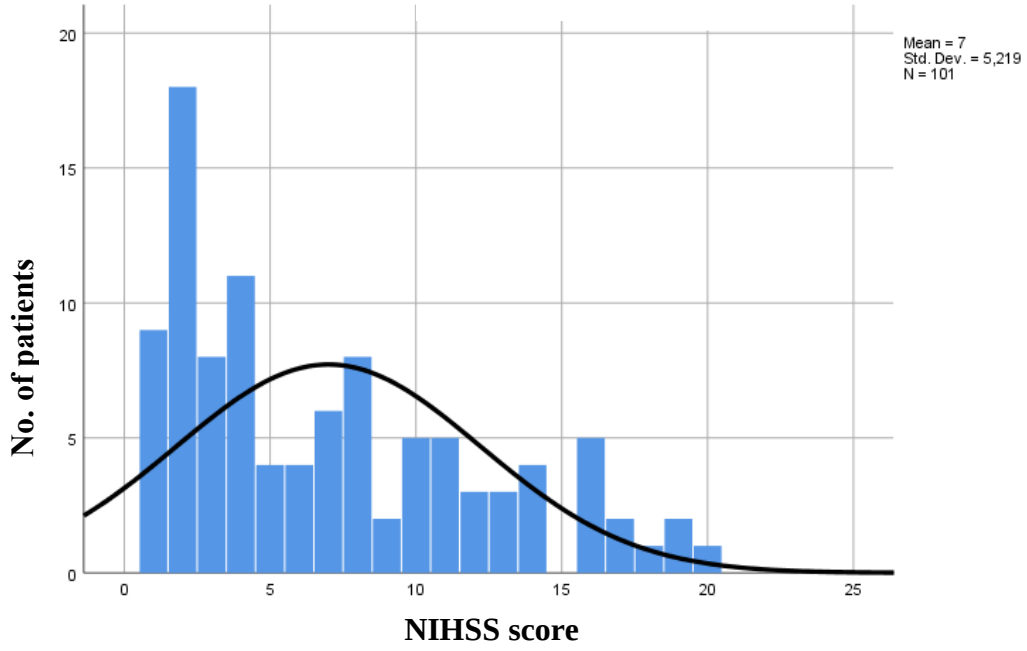

Figure 12. *Histogram illustrating the frequency distribution of NIHSS scores at admission in the control group.*

In contrast, among deceased patients (the target group), the mean NIHSS score was substantially higher - 17.07 (SD = 7.705), with a mode of 18 and values ranging from 5 to 33 (Figure 13).

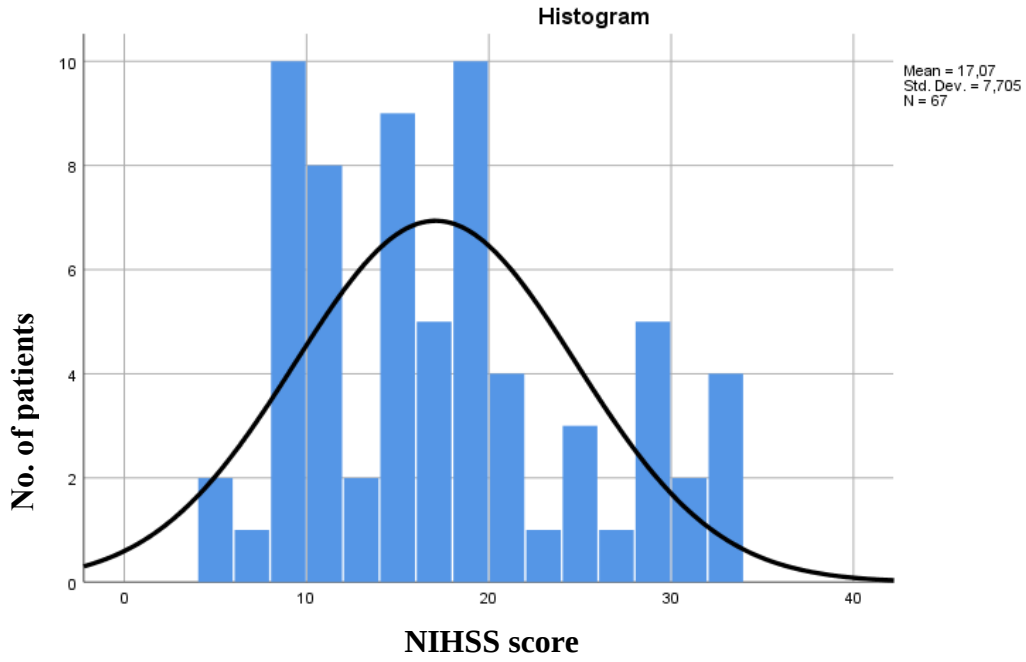

Figure 13. *Histogram illustrating the frequency distribution of NIHSS scores at admission in the target group.*

In the control group, 45 patients (44.6%) presented with a mild neurological deficit (1–4 points), an equal number (44.6%) had a moderate deficit (5–15 points), a markedly smaller proportion - 11 patients (10.9%) had a severe deficit (16–20 points), and no patients (0.0%) had a very severe deficit (≥21 points).

Among the deceased patients, admission neurological impairment was substantially worse: 32 patients (47.8%) were classified with a moderate deficit (5–15 points), 17 (25.4%) presented with a severe deficit (16–20 points), and 18 (26.9%) with a very severe deficit (≥21 points) (Figure 14).

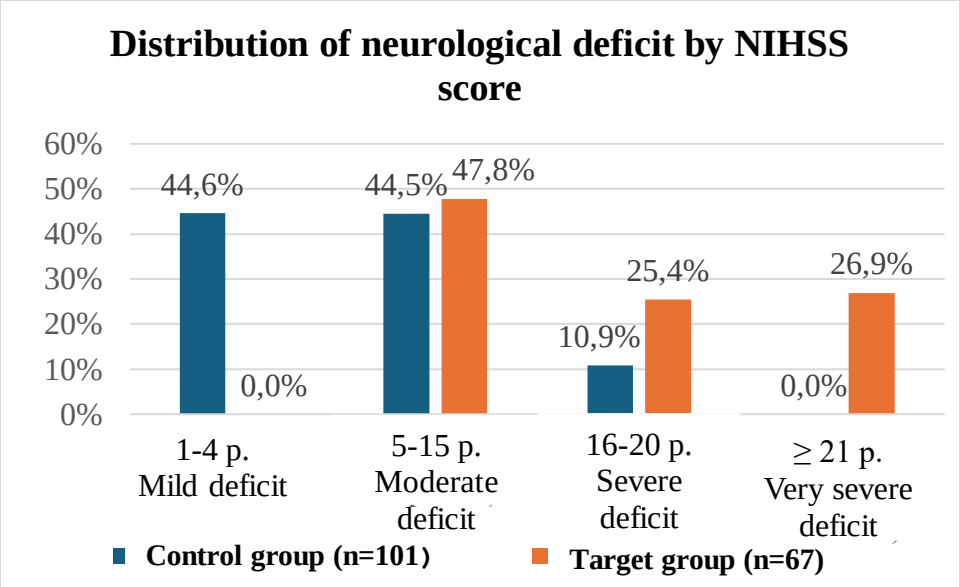

Figure 14. *Bar chart depicting the distribution of patients in the control and target groups by severity of admission neurological deficit, assessed using the NIHSS.*

To assess the association between the severity of neurological deficit (NIHSS) at admission and clinical outcome, a χ^2 test was performed. A strong statistical association was identified between admission severity and mortality ($p < 0.001$). Patients with mild and moderate deficits predominated in the control group, whereas those with severe and very severe deficits predominated in the deceased (target) group. The absence of mildly affected patients among the deceased and the substantial proportion with NIHSS ≥21 points underscore the high prognostic value of the admission NIHSS (Table 10).

Table 10. *Distribution of patients by severity of neurological deficit (NIHSS) at admission and its association with mortality.*

Severity of neurological deficit (NIHSS)	**Target group (n = 67)**	**Control group (n = 101)**	**Total (n = 168)**	**p- value**
Mild (1–4 p.)	0 (0,0%)	45 (44,6%)	45 (26,8%)	< 0,001
Moderate (5–15 p.)	32 (47,8%)	45 (44,6%)	77 (45,8%)	
Severe (16–20 p.)	17 (25,4%)	11 (10,9%)	28 (16,7%)	
Very severe (≥21 p.)	18 (26,9%)	0 (0,0%)	18 (10,7%)	

Total	67 (100%)	101 (100%)	168 (100%)	

6.1 Univariate logistic analysis of NIHSS as a predictor of mortality

To examine the association between the severity of neurological deficit at admission and fatal outcome, NIHSS scores were dichotomized at a threshold of 16 points, allocating patients to groups with lower (≤15 points) and higher (>15 points) scores. The binary logistic regression analysis demonstrated that patients with NIHSS >15 at admission had 8.95-fold higher odds of death compared with those with NIHSS ≤15 (OR = 8.949; 95% CI: 4.068–19.688; p < 0.001) (Table 11).

Table 11. *Logistic regression with dichotomized NIHSS at a 16-point threshold (mild to moderate vs severe and very severe neurological deficit).*

Independent variable	***Odds Ratio (OR)***	***95% CI***	***p-value***
NIHSS > 15 p.	8,949	4,068 – 19,688	< 0,001

7.Assessment of consciousness by the Glasgow Coma Scale (GCS) at admission as a predictor of mortality in patients with acute ischemic stroke

In the control group, the mean GCS score at admission was 13.95 (SD = 1.824), with predominantly high values (median 15). By contrast, in the target (deceased) group, the mean score was significantly lower - 10.01 (SD = 3.466) indicating greater dispersion of results and a tendency toward lower scores (Figures 15 and 16).

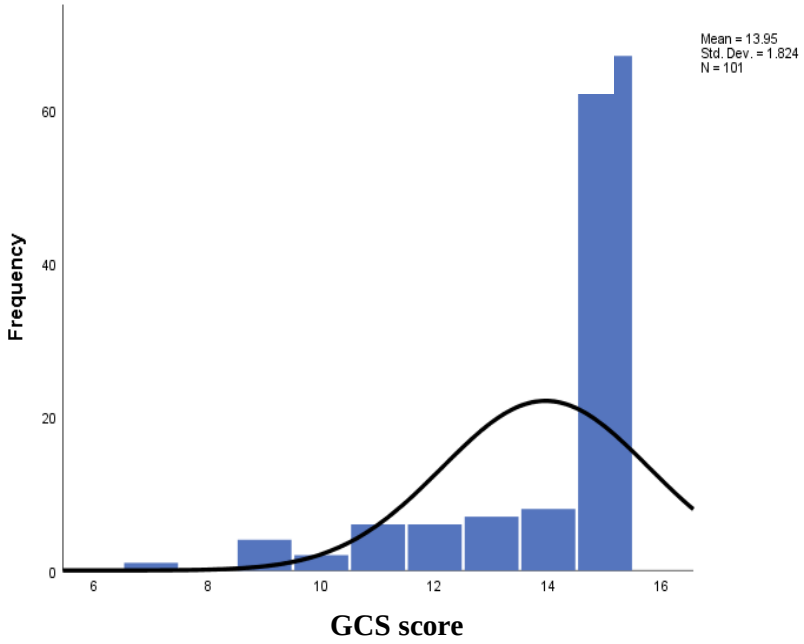

Figure 15. *Histogram illustrating Glasgow Coma Scale scores at admission - control group.*

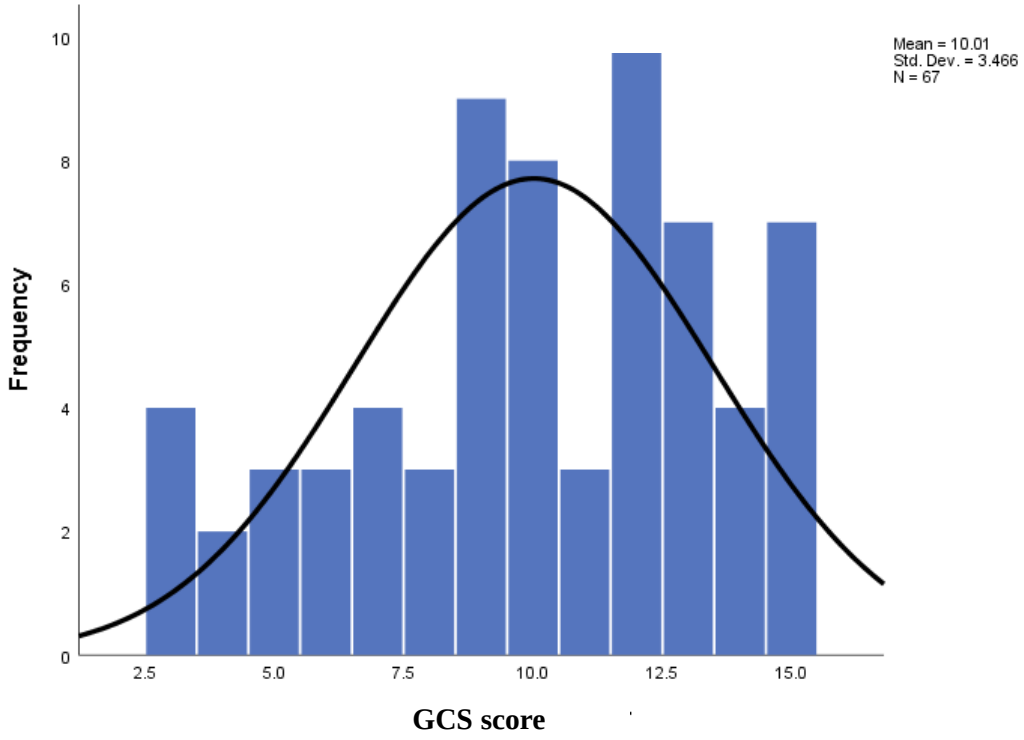

Figure 16. *Histogram illustrating Glasgow Coma Scale scores at admission - target group.*

The comparative analysis of GCS revealed substantial differences in the level of consciousness between groups. In the control group, patients with the maximum score of 15 predominated (66.3% of cases). Overall, 81.2% of survivors had scores of 13–15, whereas only 18.8% scored below 13.
In the target (deceased) group, the distribution was markedly shifted toward lower values, only 10.4% achieved the maximum score of 15. In total, 68.7% had scores below 13, and 28.4% scored below 9. These findings clearly demonstrate the association between lower GCS at admission and fatal outcome (Figure 17).

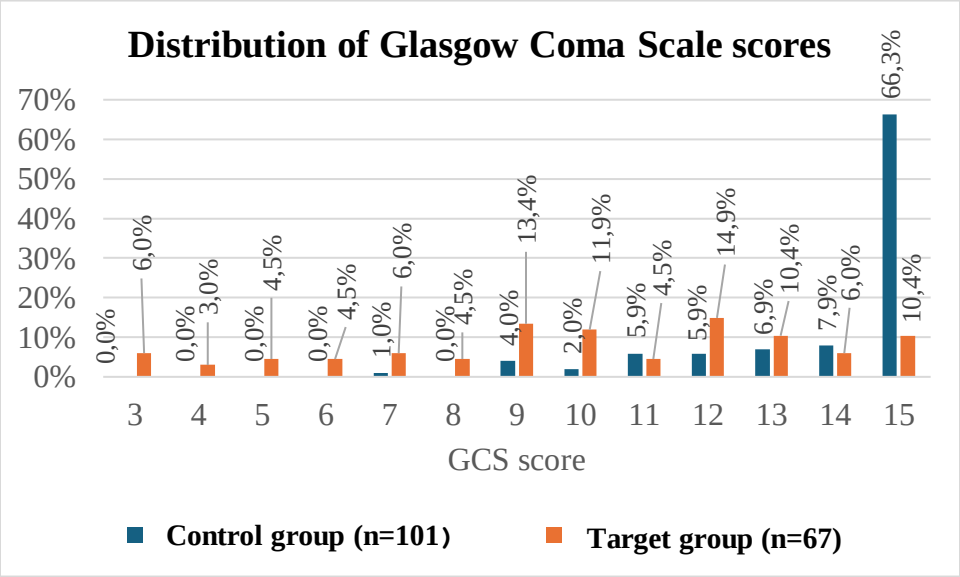

Figure 17. *Bar chart showing the percentage distribution of Glasgow Coma Scale scores at admission in the control and target groups.*

The χ^2 analysis revealed a statistically significant association between admission GCS and mortality ($p < 0.001$). The test for linear-by-linear association ($p < 0.001$) further underscored a clear linear trend: as GCS decreases, the proportion of patients with a fatal outcome increases (Table 12).

Table 12. *Results of the χ^2 analysis for the association between group and Glasgow Coma Scale scores.*

Statistical test	**Value**	**Degrees of freedom (df)**	**p-value**
Pearson χ^2 test	70,304	12	< 0,001

Likelihood ratio (LR)	81,267	12	< 0,001
Linear-by-Linear association	59,549	1	< 0,001

7.1 Univariate logistic analysis of the Glasgow Coma Scale (GCS) at admission as a predictor of mortality in patients with acute ischemic stroke

On clinical grounds, the GCS was dichotomized at a threshold of 13 points (GCS ≤12 vs GCS ≥13). The binary logistic regression analysis showed that the severity of impaired consciousness at admission is a strong predictor of mortality. Patients with GCS ≤12 had 31.25-fold higher odds of death compared with those with GCS ≥13 (OR = 31.25; 95% CI: 4.05–250; p < 0.001) (Table 13).

Table 13. *Logistic regression with dichotomized GCS at a 13-point threshold (moderate–severe vs mild impairment of consciousness).*

Independent variable	Odds Ratio (OR)	95% CI	p-value
GCS ≤12 vs. GCS >12	31,25	4,05 – 250,0	< 0,001

Vital parameters at admission as predictors of mortality in patients with acute ischemic stroke

8.1 Systolic blood pressure at admission as a prognostic factor for mortality

The descriptive analysis of systolic blood pressure (SBP) showed similar mean values between groups (144.40 mmHg in the control group vs 141.97 mmHg in the target group). The larger standard deviation in the target group (SD = 35.775 vs SD = 24.868) indicates a wider distribution and the presence of extreme values. This variability is clinically relevant: the lowest value in the target group was 80 mmHg (consistent with hypoperfusion and poor prognosis), compared with 90 mmHg in the control group. Maximum values were also higher among those

with a fatal outcome (240 mmHg vs 220 mmHg), underscoring a bidirectional risk (hypotension and extreme hypertension) in the acute phase.

The comparative analysis of SBP categories revealed significant differences. In the target group (n = 67), the highest frequencies were observed in the <120 mmHg and 140–159 mmHg categories (26.9% each). Values ≥180 mmHg were recorded in 17.8% of deceased patients. In the control group (n = 101), the most common categories were 140–159 mmHg (28.7%) and 130–139 mmHg (21.8%). The <120 mmHg category accounted for 9.9%, and ≥180 mmHg for 11.9%. These findings indicate that extreme values, particularly hypotension were more pronounced in the mortality group (Figure 18).

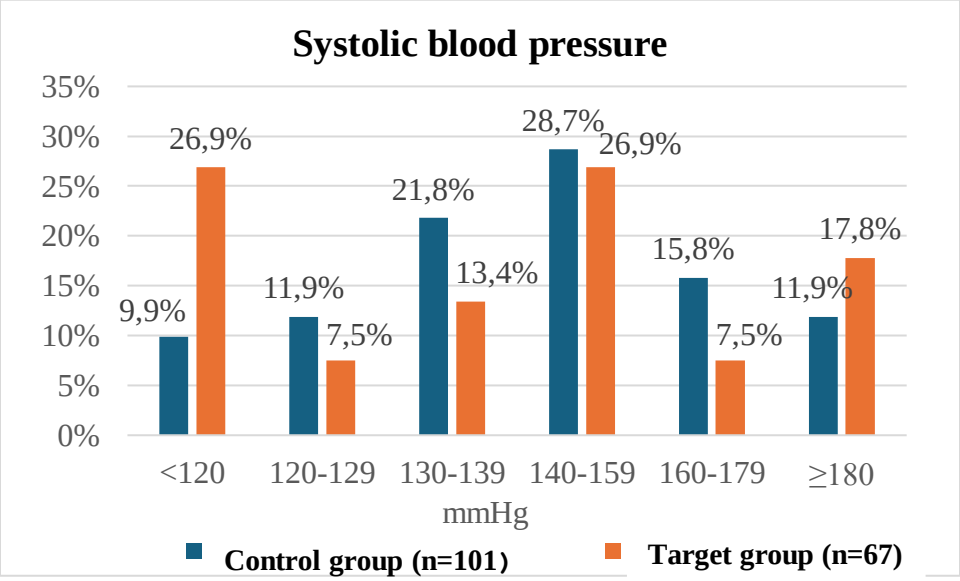

Figure 18. *Bar chart showing the percentage distribution of patients by systolic blood pressure categories at admission in the control and target groups.*

The comparative χ^2 analysis of SBP category distributions revealed a statistically significant association between admission SBP and mortality ($p = 0.028$). The highest relative proportion of fatal outcomes occurred in the <120 mmHg group (64.3% of cases) and in the hypertensive crisis group ≥180 mmHg (50.0% of cases), highlighting a U-shaped risk pattern. The absence of a statistically significant linear trend ($p = 0.235$) suggests that risk concentrates within specific critical ranges rather than increasing progressively (Table 14).

Table 14. *Results of the χ^2 analysis for the association between systolic blood pressure (SBP) categories at admission and mortality.*

Statistical test	Value	| Degrees of freedom (df)	p-value

Pearson χ^2 test	12,591	5	0,028
Likelihood ratio (LR) χ^2	12,641	5	0,027
Linear-by-linear association	1,411	1	0,235

To evaluate the prognostic value of extremely low and exceptionally high SBP at admission, two separate χ^2 analyses were performed using dichotomized variables. Dichotomization at <120 mmHg revealed a statistically significant association with mortality (p = 0.006). The highest relative proportion of deaths (64.3%) was observed among individuals with low SBP. The univariate logistic analysis showed that patients with SBP <120 mmHg had 3.4-fold higher odds of death compared with those with normal or elevated SBP (OR = 3.400; 95% CI: 1.378–8.387). At the ≥180 mmHg threshold, the χ^2 test did not demonstrate a statistically significant association with mortality (p = 0.274). Although the estimated odds ratio (OR = 1.618; 95% CI: 0.679–3.854) suggested a slight trend toward increased risk, the wide confidence interval precluded statistical significance. Therefore, extremely high SBP at admission cannot be interpreted as an independent predictor of mortality in this cohort (Table 15).

Table 15. *Results of χ^2 analyses and estimated odds ratios for different dichotomizations of systolic blood pressure (SBP) at admission.*

Dichotomization of SBP	**χ^2 (df)**	**p-value**	**Likelihood Ratio (p)**	**Linear-by-Linear Association (p)**	**Odds Ratio (95% CI)**
<120 mmHg vs ≥120 mmHg	7,424 (1)	0,006	7,399 (p = 0,007)	7,354 (p = 0,007)	3,400 (1,378 - 8,387)
≥180 mmHg vs <180 mmHg	1,196 (1)	0,274	1,175 (p = 0,278)	1,189 (p = 0,276)	1,618 (0,679-3,854)

8.2 Heart rate at admission as a prognostic factor for mortality

In the target group, the mean heart rate (HR) at admission was 90.28 beats/min (mode 100 beats/min). The high standard deviation - 20.90 indicates wide dispersion and heterogeneity, with values ranging from 54 to 150 beats/min.
In the control group, the mean HR was significantly lower - 75.06 beats/min (mode 80 beats/min). The markedly lower standard deviation of 11.41 suggests more homogeneous HR values among survivors.

When HR was categorized into three groups, tachycardia (>100 beats/min) showed a strong association with fatal outcome. Among all patients with tachycardia, 82.4% belonged to the mortality group, whereas 81.8% of those with bradycardia (<60 beats/min) survived. The χ^2 test confirmed a significant association between admission HR and clinical outcome ($p < 0.001$). The linear-by-linear association ($p < 0.001$) is particularly informative, demonstrating a monotonic increase in mortality risk with rising heart rate (Table 16).

Table 16. *Distribution of patients by heart rate at admission and clinical outcome.*

HR	Total (n)	Control group (N, %)	Target group (N, %)	p-value
<60 beats/min	11	9 (81,8%)	2 (18,2%)	p < 0,001
60–100 beats/min	140	89 (63,6%)	51 (36,4%)	
>100 beats/min	17	3 (17,6%)	14 (82,4%)	
Total	168	101 (60,1%)	67 (39,9%)	

It should be noted that, due to the small number of cases with bradycardia (n = 11), inferences for this subgroup should be interpreted with caution.
The logistic analysis showed that tachycardia (≥100 beats/min) at admission was associated with a significantly increased risk of death. Patients with tachycardia had 11.86-fold higher odds of mortality compared with those with HR <100 beats/min (OR = 11.856; 95% CI: 3.859–36.426; $p < 0.001$), underscoring elevated heart rate as an independent predictor of adverse outcome (Table 17).

Table 17. *Odds ratio for tachycardia at admission as a predictor of mortality in ischemic stroke patients under 59 years of age.*

Values compared	Odds Ratio (OR)	95% CI	p-value
HR ≥100 beats/min vs <100 beats/min	11,856	3,859-36,426	< 0,001

9.Neuroimaging findings as prognostic factors for mortality in young and middle-aged patients with acute ischemic stroke

9.1 Frequency distribution by ASPECTS in patients with ischemic stroke

The ASPECTS was calculated only for patients in whom ischemic changes were visualized on admission computed tomography. In the control group, the mean score was 7.93 (SD = 1.265; mode 9). In the mortality group, the mean score was significantly lower - 7.09 (SD = 1.774; mode 8). The lower mean, greater dispersion, and presence of extremely low values (minimum 3 vs 5) in the target group indicate greater severity and heterogeneity of early ischemic changes, which is associated with poor outcome (Figures 19 and 20).

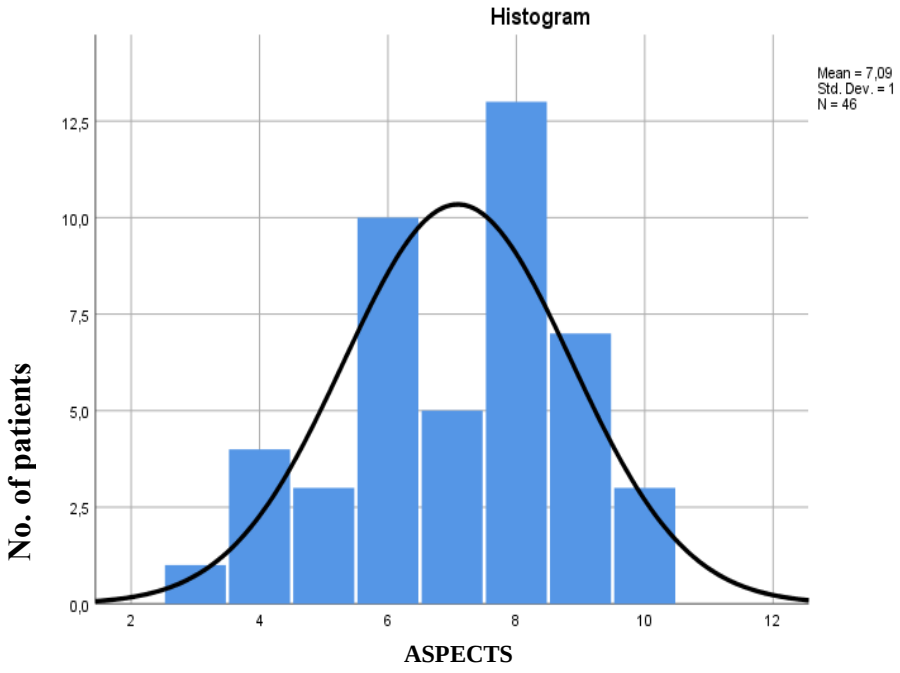

Figure 19. *Histogram illustrating the distribution of ASPECTS scores in the target group.*

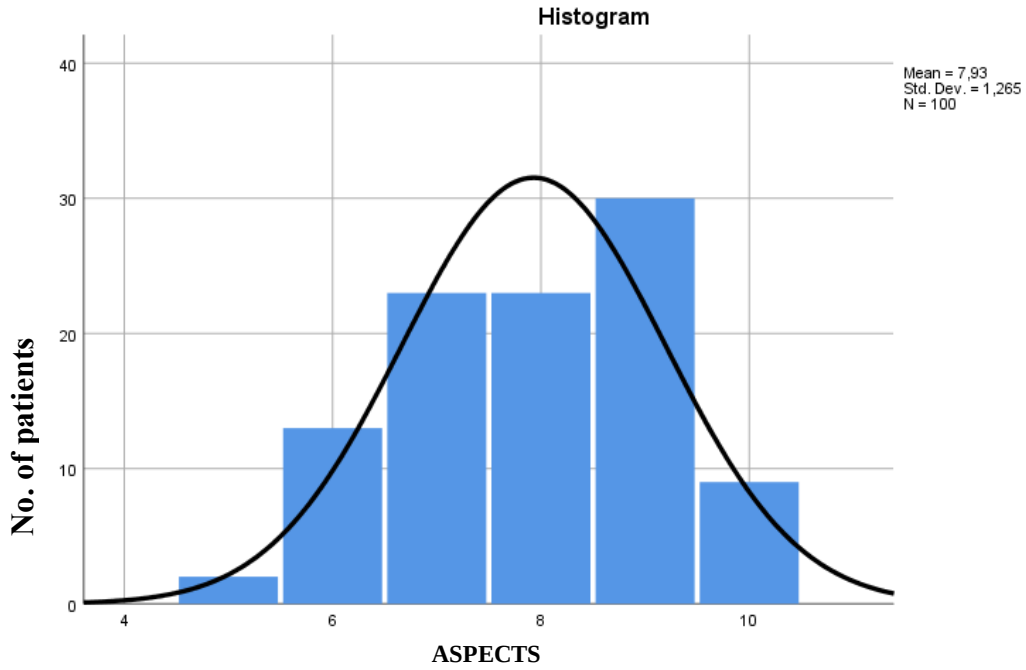

Figure 20. *Histogram illustrating the distribution of ASPECTS scores in the control group.*

9.2 Frequency distribution by stroke localization

The analysis of stroke localization showed a higher relative proportion of posterior circulation strokes in the target (deceased) group (44.7%) compared with the control group. Within the anterior circulation, 34.4% of deceased patients had right-hemispheric involvement.
By comparison, in the control group, the posterior circulation was affected in 36.6% of cases. Among survivors with anterior circulation involvement, left-hemispheric strokes predominated (36.6%), whereas right-hemispheric involvement was observed in 26.8% (Figure 21).

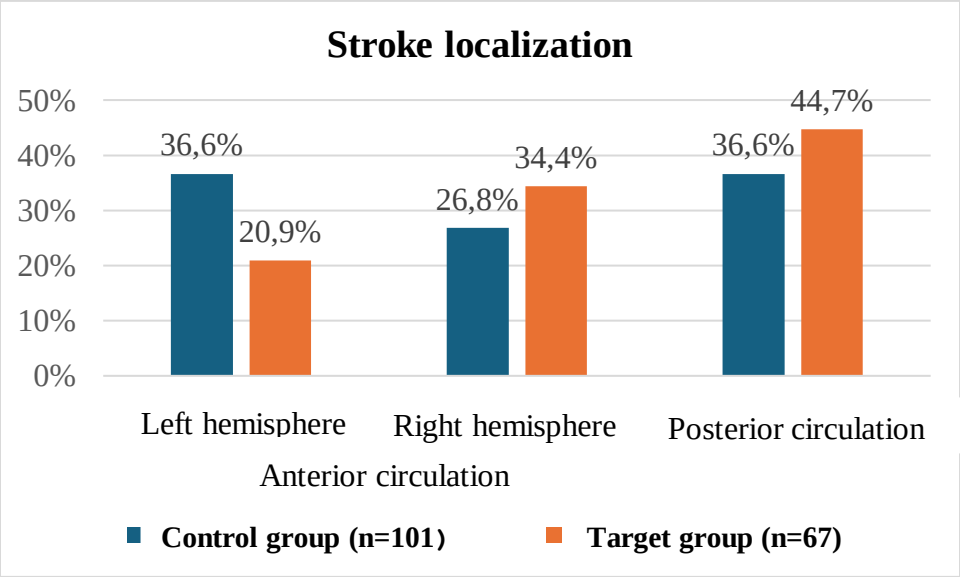

Figure 21. *Bar chart showing the distribution of patients in both groups by affected vascular territory.*

9.3 Frequency distribution by the presence of a hyperdense middle cerebral artery (MCA)

In the mortality group (n = 67), a hyperdense MCA was identified in 13.4% of patients (n = 9), whereas the majority (86.6%; n = 58) had no such finding.
In the control group (n = 101), a hyperdense MCA was present in 18.8% of cases (n = 19) and absent in 81.2% (n = 82) (Figure 22).

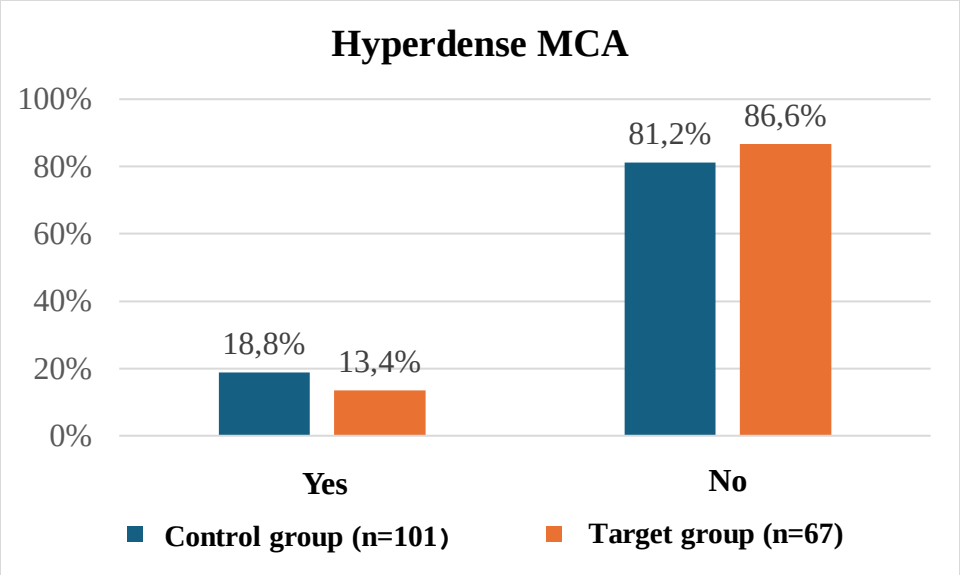

Figure 22. *Bar chart illustrating the distribution of patients by the presence of a hyperdense MCA in the control and target groups.*

9.4 Comparative and univariate analysis of imaging findings (ASPECTS, localization, and hyperdense middle cerebral artery) as predictors of mortality in patients with acute ischemic stroke

The univariate analysis of the dichotomized ASPECTS (≤7 vs >7 points) did not demonstrate a statistically significant association with mortality ($\chi^2 = 1.865$, $p = 0.172$). Nonetheless, a trend was observed whereby patients with ASPECTS ≤7 had 1.63-fold higher odds of death (95% CI: 0.812–3.323), though this did not reach statistical significance.

Analysis by vascular territory (anterior vs posterior circulation) likewise did not show a significant association with mortality ($p = 0.291$). Patients with anterior-circulation infarcts had 0.713-fold lower odds of death compared with those with posterior-circulation infarcts (95% CI: 0.380–1.338), but this result was also not statistically significant.

The analysis revealed a strong trend toward a statistically significant association between stroke lateralization and mortality ($p = 0.053$). Right-hemispheric infarction was associated with a lower likelihood of survival: patients with left-hemispheric infarcts had 2.25-fold higher odds of survival compared with those with right-sided infarcts (OR = 2.251; 95% CI: 0.983–5.159), although this finding did not meet the threshold for statistical significance.

No statistically significant association was found between the presence of a hyperdense MCA and mortality ($p = 0.360$). The odds ratio (OR = 1.493) suggested a slight but non-significant tendency toward increased odds of death in the presence of this finding (Table 18).

Table 18. *Prognostic value of imaging findings for mortality in ischemic stroke.*

Predictor	p-стойност	OR	95 %CI
ASPECTS	0,172	1,630	0,812 – 3,323
Vascular territory	0,291	0,713	0,380–1,338
Lateralization	0,053	2,251	0,983 – 5,159
Hyperdense MCA	0,360	1,493	0,631 – 3,534

10. Laboratory markers at admission as predictors of mortality in patients with acute ischemic stroke

10.1 Distribution of C-reactive protein (CRP) values at admission

This analysis examined C-reactive protein (CRP), leukocyte count, serum glucose, and sodium levels at hospital admission, comparing patients with a fatal outcome (n = 67) to the control group (n = 101). The mean CRP level was markedly higher in the mortality group (mean = 51.56 mg/L; SD = 83.03) than in the control group (mean = 11.01 mg/L; SD = 21.17). The distributions in both groups were highly positively skewed, indicating the presence of extremely elevated values particularly in the mortality group. Kurtosis was also high, suggesting a sharply peaked distribution with heavy tails, a pattern typical of an inflammatory response in severely ill patients (Table 19, Figures 23 and 24).

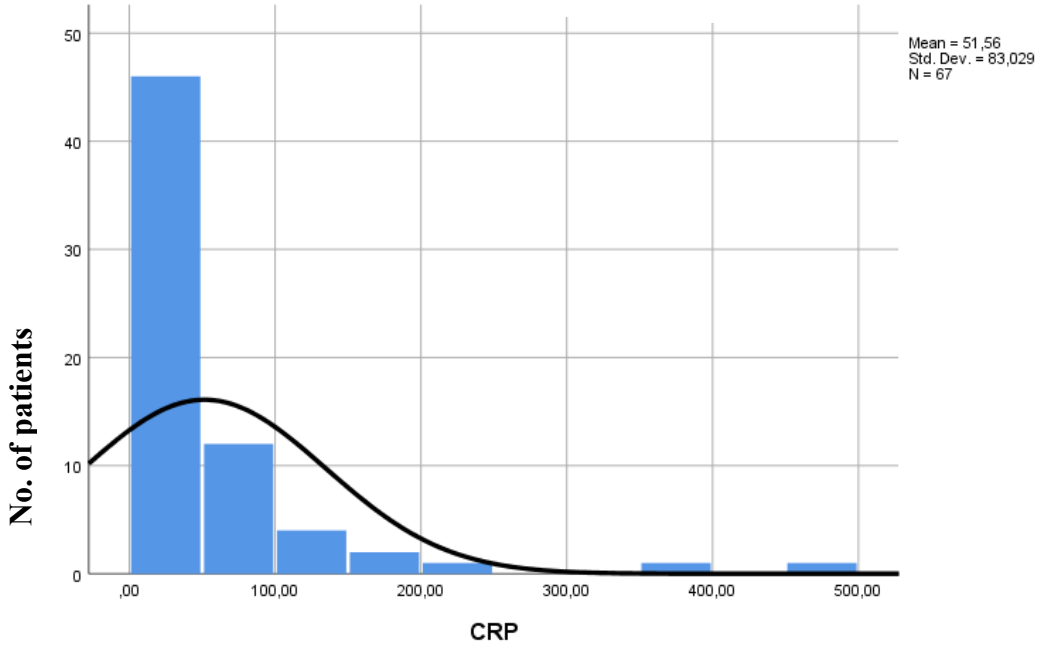

***Figure 23**. Histogram illustrating the distribution of patients by CRP values in the target group*

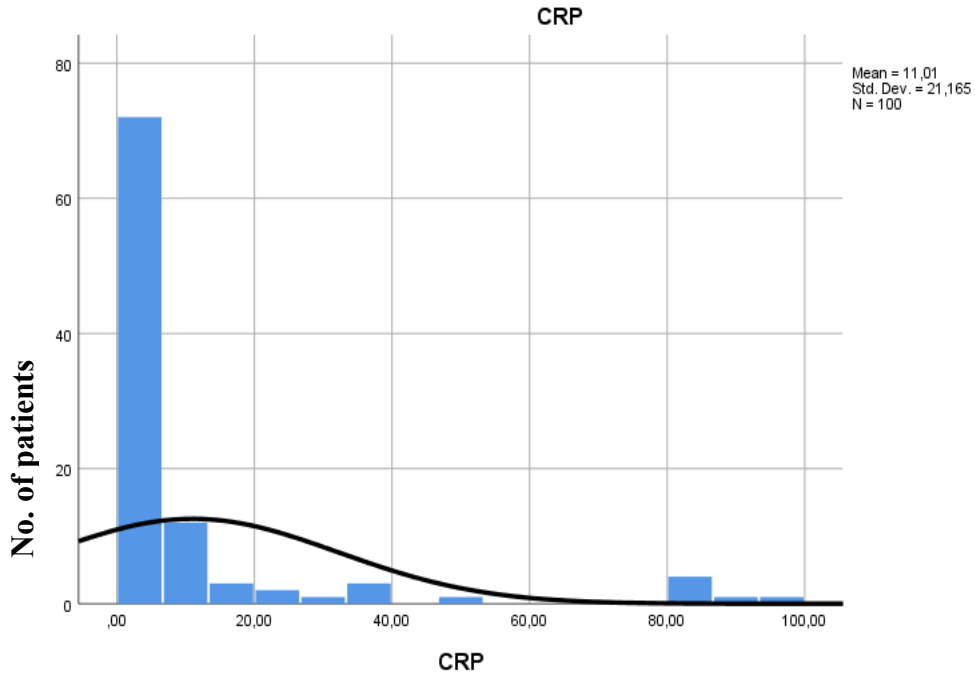

***Figure 24.** Histogram illustrating the distribution of CRP values in the control group.*

10.2 Distribution of leukocyte counts at admission

The mean leukocyte count was higher in the mortality group (mean = 12.39 × 10^9/L; SD = 5.98) compared with the control group (mean = 9.88 × 10^9/L; SD = 2.87). A positive skew was also observed here, with substantially lower variability in the control group. Kurtosis was close to normal, suggesting a more moderate distribution (Table 19, Figures 25 and 26).

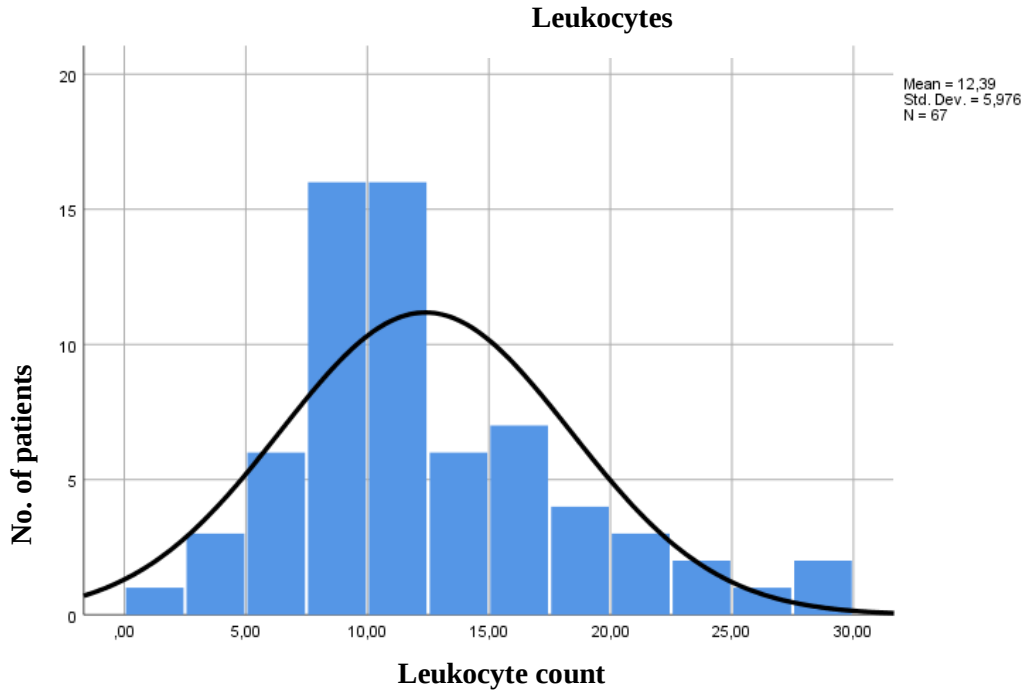

Figure 25. *Histogram illustrating the distribution of patients by leukocyte count in the target group.*

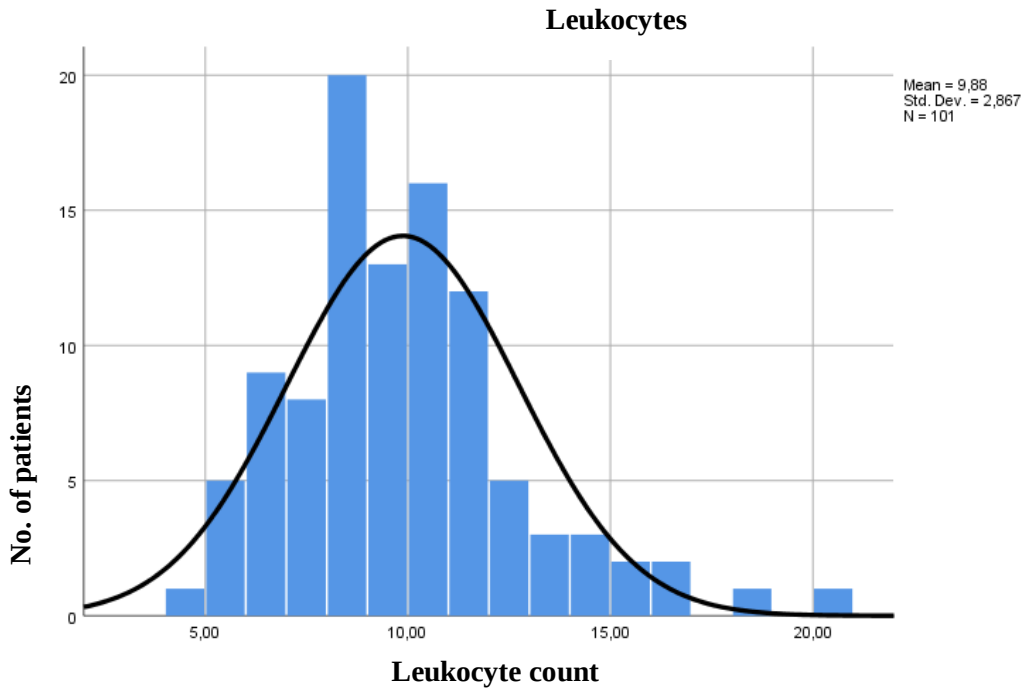

Figure 26. *Histogram illustrating the distribution of patients by leukocyte count in the control group.*

10.3 Distribution of serum glucose levels at admission

Serum glucose levels at admission were higher in the mortality group (mean = 9.65 mmol/L; SD = 4.58) than in the control group (mean = 7.56 mmol/L; SD = 4.97). In the control group, the distribution was highly positively skewed with elevated kurtosis, suggesting the presence of isolated extremely high values. In the target group, the distribution was more moderate (Figures 27 and 28, Table 19).

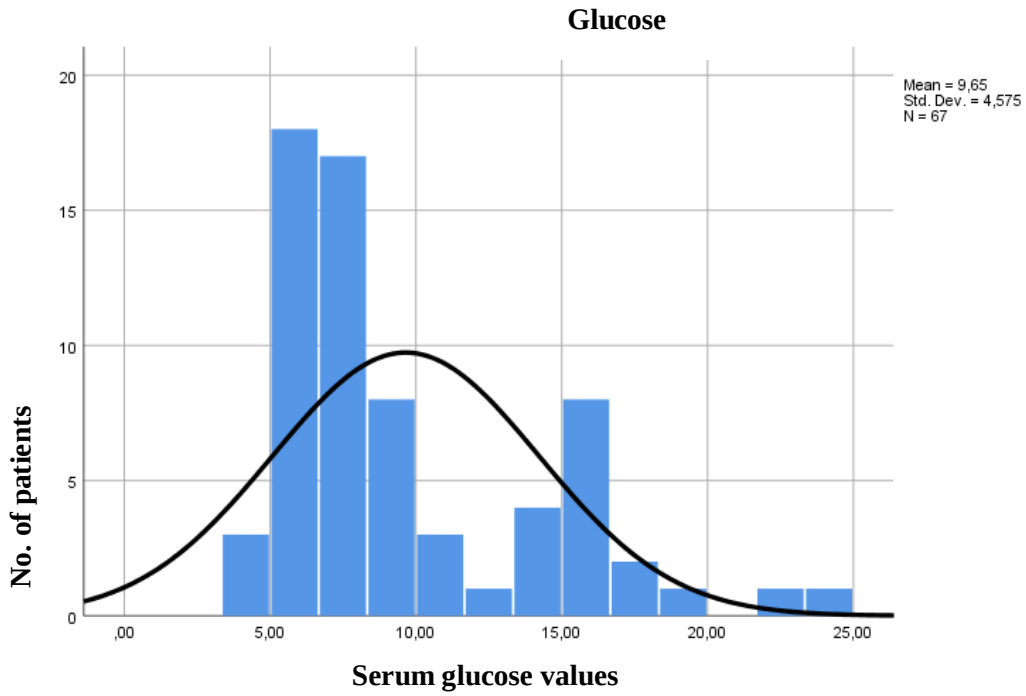

Figure 27. *Histogram illustrating the distribution of patients by serum glucose values in the target group.*

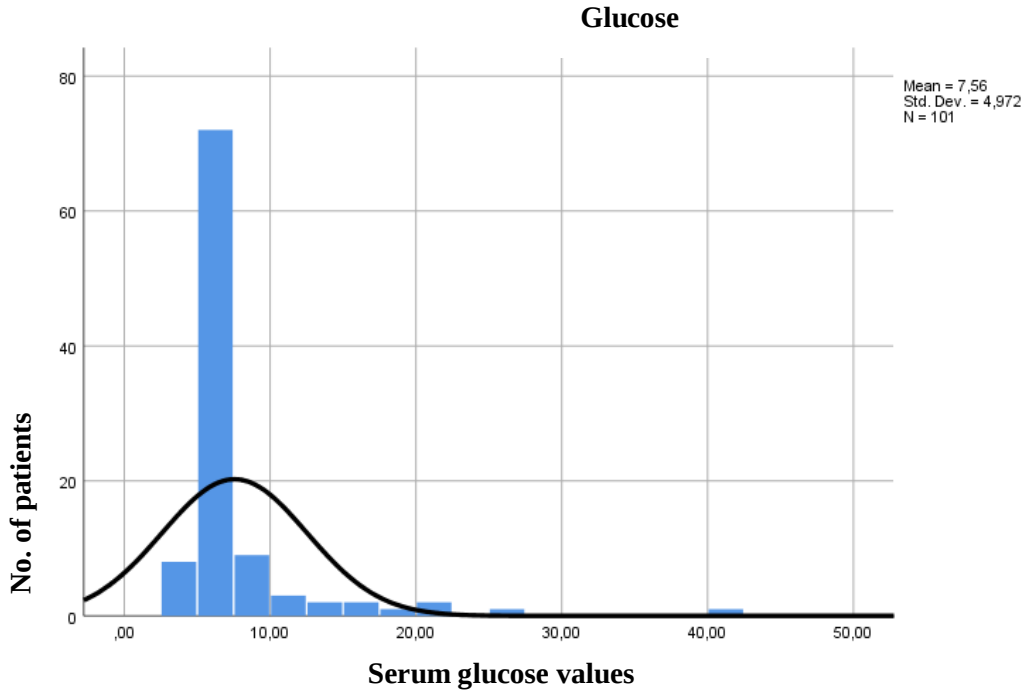

Figure 28. *Histogram illustrating the distribution of patients by serum glucose values in the control group.*

10.4 Distribution of serum sodium levels at admission

Sodium levels were similar between groups. In the target group, the mean was 138.49 mmol/L (SD = 7.46), and in the control group, 138.54 mmol/L (SD = 3.41). The distributions in both groups were approximately normal; however, the mortality group exhibited a wider range of values (minimum 109, maximum 169 mmol/L). (Figures 29 and 30, Table 19).

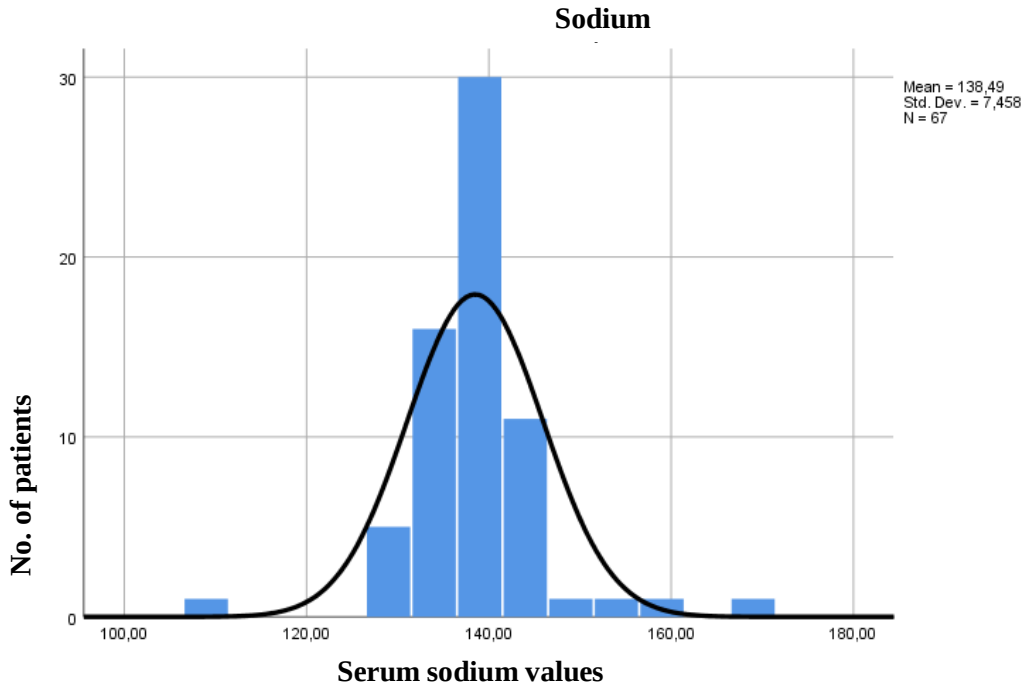

Figure 29. *Histogram illustrating the distribution of patients by serum sodium values in the target group.*

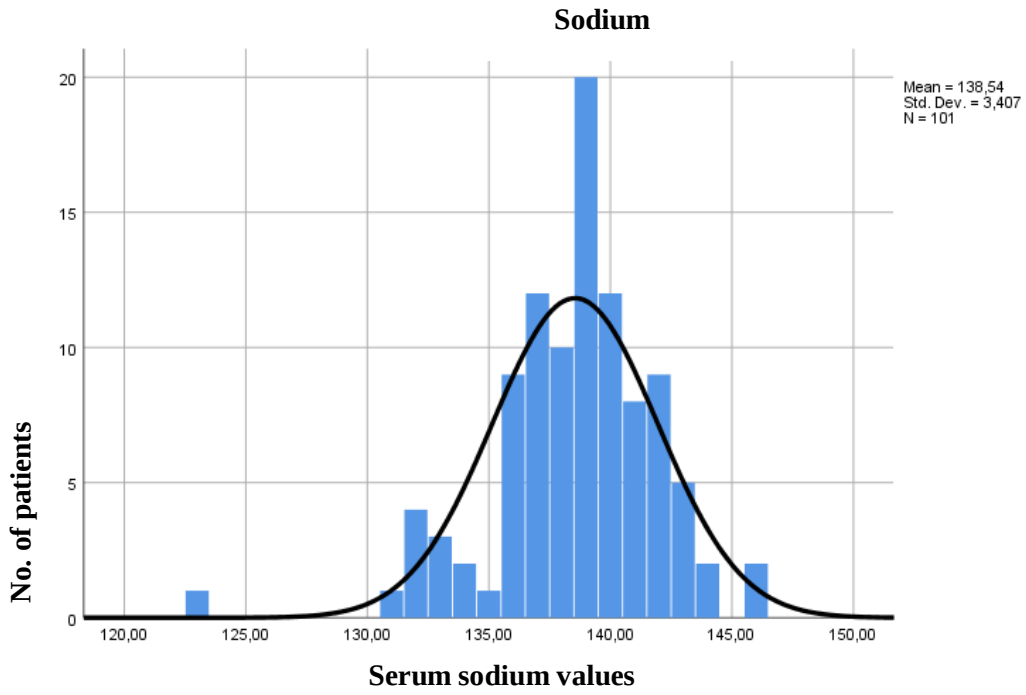

Figure 30. *Histogram illustrating the distribution of patients by serum sodium values in the control group.*

Table 19. *Descriptive statistics of laboratory markers at admission in the target and control groups*

	Target group (n=67)				Control group (n=101)			
Indicator	**CRP**	**Leukocytes**	**Glucose**	**Sodium**	**CRP**	**Leukocytes**	**Glucose**	**Sodium**
Mean value	51,56	12,36	9,64	138,49	11,01	9,87	7,55	138,54
Standard deviation	83,02	5,97	4,57	7,45	21,16	2,86	4,97	3,407
Minimum value	41,0	15,0	3,80	109,0	19,0	4,49	3,70	123,0
Maximum value	488,58	28,83	24,0	169,0	99,95	20,96	42,0	146,0
Skewness	3,256	0,782	1,179	0,588	2,950	1,016	4,403	-1,062

Standard error of skewness	0,293	0,293	0,293	0,293	0,241	0,240	0,240	0,240
Kurtosis	13,119	0,407	0,700	7,456	8,054	2,115	24,52	3,588
Standard error of kurtosis	0,578	0,578	0,578	0,578	0,478	0,476	0,476	0,476

10.5 Comparative analysis of admission laboratory parameters as predictors of mortality

The analysis of CRP demonstrated a statistically significant difference between the mortality group and the controls ($p < 0.001$). The mean rank for CRP was markedly higher in the target group than among survivors, underscoring the role of systemic inflammatory response in fatal outcomes.

Similarly, leukocyte counts at admission also differed significantly between groups ($p = 0.012$). Patients with a fatal outcome exhibited higher leukocyte levels compared with controls, reflecting an accentuated inflammatory response in fatal cases.

Serum glucose at admission likewise showed significant prognostic value, with a clear difference between groups ($p < 0.001$): patients with a fatal outcome had substantially higher glucose levels than survivors. This finding supports the hypothesis that hyperglycemia adversely affects outcomes in the acute phase of ischemic stroke.

In contrast, serum sodium did not differ significantly between groups ($p = 0.261$).

Table 20. Results of the Mann–Whitney U test for laboratory parameters at admission.

Indicator	**Mean Rank Control group (n=101)**	**Mean Rank Target group (n=67)**	**p-value**
CRP	67,29	108,95	< 0,001
Leukocytes	76,85	96,03	0,012
Glucose	70,60	105,45	< 0,001
Sodium	87,92	79,35	0,261

11. Additional factors as predictors of mortality in patients with acute ischemic stroke

11.1 Treatment as a predictor of mortality

Analysis of treatment distribution across the two study groups showed that, in the mortality group, the majority - 94.0% were managed without thrombolysis, while only 6.0% received thrombolytic therapy.
A similar pattern was observed in the control group, where 93.1% of patients did not undergo thrombolysis and 6.9% were treated with thrombolysis (Figure 31).

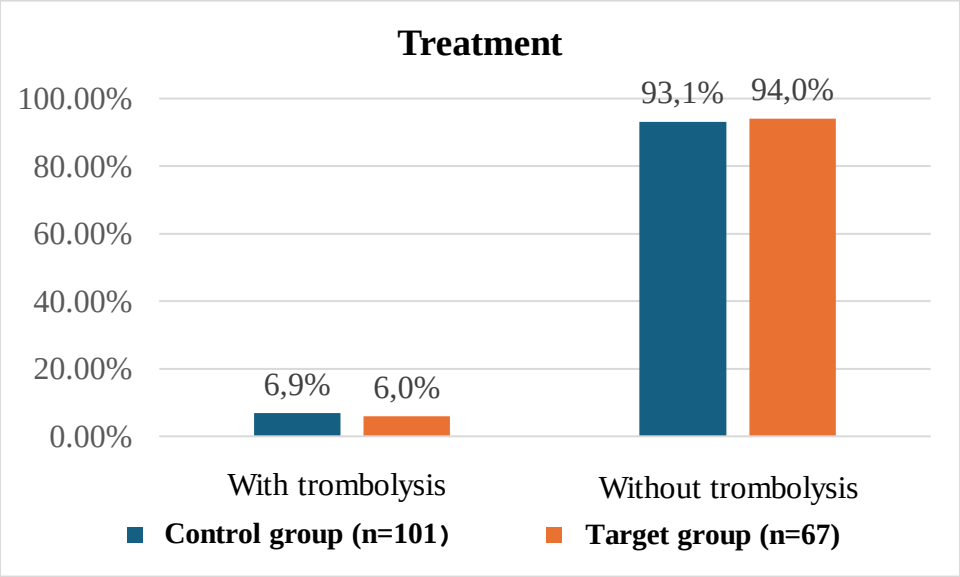

Figure 31. *Bar chart showing the distribution of patients in both groups according to the treatment administered.*

The distribution of patients by receipt of intravenous thrombolysis did not show a statistically significant association with mortality in ischemic stroke patients under 60 years of age (p = 0.805). The odds-ratio analysis likewise revealed no significant association. These findings do not support a relationship between thrombolytic therapy and mortality in the study population. Results should be interpreted with caution due to the small number of patients treated with thrombolysis in both groups (Table 21).

Table 21. *Odds ratio (OR) for mortality according to treatment administered.*

Indicator	p-value	OR	95 %CI
Type of treatment	0,805	1,161	0,354 – 3,812

11.2 Length of hospitalization as a predictor of mortality

The Mann–Whitney U test demonstrated a statistically significant difference in length of hospital stay between the two groups ($p < 0.001$). Survivors had a substantially longer hospitalization compared with patients with a fatal outcome (Table 22).

Table 22. *Results of the Mann–Whitney U test for length of hospitalization (days).*

Indicator	Mean Rank Control group (n=101)	Mean Rank Target group (n=67)	p-value
Length of hospitalization (days)	97,67	64,65	p < 0,001

12.Multivariable logistic regression analysis of significant predictors of mortality in patients with acute ischemic stroke aged ≤59 years

To evaluate the independent prognostic value of various clinical characteristics, comorbidities, and laboratory parameters in patients aged ≤59 years with ischemic stroke, a multivariable binary logistic regression analysis was performed. The models incorporated both dichotomized categorical variables and continuous predictors: age, C-reactive protein (CRP), leukocyte count at admission, serum glucose, length of hospitalization (days), and number of comorbidities.
To avoid overfitting and multicollinearity, the analysis was structured into four separate regression models (Model A, Model B, Model C, and Model D). Model D includes only those

variables that demonstrated independent statistical significance ($p < 0.05$) in at least one of the three preceding multivariable models.

12.1 Model A: Comorbidities as predictors of mortality - logistic regression

Model A included: age, chronic left-sided heart failure, acute inflammatory disease at admission, diabetes mellitus, dyslipidemia, prior stroke, prior myocardial infarction, ischemic heart disease, and deep-vein thrombosis.
The model showed good overall fit and explained up to 53.5% of the variance in mortality.

Significant predictors:

Age: A statistically significant positive association was observed between age and the probability of death ($p = 0.033$). The adjusted odds ratio (AOR = 1.071; 95% CI: 1.006–1.141) indicates that each additional year of age increases the odds of death by 7.1%.

Chronic left-sided heart failure: Presence of chronic left-sided heart failure was independently associated with markedly higher odds of death (AOR = 7.30; $p < 0.001$), corresponding to approximately 7.3-fold greater odds compared with patients without this condition.

Acute inflammatory disease at admission: An acute inflammatory process on admission was independently associated with increased mortality risk (AOR = 7.25; $p = 0.001$), corresponding to roughly 7.2-fold higher odds of death.

Non-significant predictors: diabetes mellitus ($p = 0.582$), dyslipidemia ($p = 0.070$), prior stroke ($p = 0.578$), prior myocardial infarction ($p = 0.132$), ischemic heart disease ($p = 0.135$), and deep-vein thrombosis ($p = 0.227$).

Table 23. *Results of multivariable binary logistic regression for comorbidities associated with mortality in patients with ischemic stroke aged ≤59 years.*

Variable	B (coefficient)	Standard error	Wald $\chi 2$	df	p-value	AOR [Exp(B)]	95 % CI
DM	-0,281	0,511	0,304	1	0,582	0,755	0,277 - 2,053

Dyslipidemia	0,871	0,481	3,282	1	0,070	2,389	0,931 - 6,129
Age	0,069	0,032	4,569	1	0,033	1,071	1,006 - 1,141
Prior stroke	-0,554	0,996	0,310	1	0,578	0,574	0,082 - 4,047
Prior MI	-1,511	0,996	2,271	1	0,132	0,221	0,031 - 1,575
IHD	-0,907	0,607	2,236	1	0,135	0,404	0,123 - 1,326
CLHF	1,998	0,471	17,79	1	<0,001	7,321	2,921 - 18,521 *
DVT	-1,052	0,870	1,460	1	0,227	0,349	0,063 - 1,924

Acute inflammatory process	1,981	0,577	11,769	1	0,001	7,253	2,34–22,73
Constant	1,438	2,238	0,413	1	0,521	4,212	N/A

CI – confidence interval;
AOR – adjusted odds ratio.

12.2 Model B: Clinical and laboratory parameters at admission as predictors of mortality

Model B included: age, NIHSS (>15 vs ≤15), GCS (≤12 vs >12), systolic blood pressure (SBP ≤120 mmHg), heart rate (>100 beats/min), CRP, and serum glucose.

The overall prognostic performance of the model was statistically significant ($p < 0.001$), with a classification accuracy of 84.4%.

Significant predictors:

NIHSS >15 points: the strongest independent predictor (AOR = 7.204; 95% CI: 2.646–19.613; $p < 0.001$), increasing the odds of death more than sevenfold.

Heart rate >100 beats/min: AOR = 7.738; 95% CI: 2.110–28.382; $p = 0.002$, indicating 7.7-fold higher odds of mortality.

SBP ≤120 mmHg: AOR = 3.695; 95% CI: 1.063–12.846; $p = 0.040$, corresponding to 3.7-fold higher odds of death.

Age: AOR = 1.071; 95% CI: 1.006–1.141; $p = 0.037$; each additional year increases the odds of death by 7.1%.

CRP: Each 1 mg/L increase in CRP is associated with ~1.8% higher odds of death (AOR = 1.018; $p = 0.011$), suggesting that higher admission CRP is linked to increased mortality risk.

Non-significant predictors: GCS ≤12 points ($p = 0.177$); Serum glucose ($p = 0.193$)

Table 24. *Results of the multivariable logistic regression analysis (Model B): clinical, hemodynamic, neurological, and laboratory predictors of mortality in ischemic stroke patients under 59 years of age.*

Variable	B (coefficient)	Standard error	Wald $\chi 2$	p-value	AOR [Exp(B)]	95 % CI

Age	0,073	0,035	4,337	0,037	1,071	1,006-1,141
NIHSS > 15 т.	1,975	0,511	14,933	<0,001	7,204	2,646 – 19,613
GCS ≤ 12 т.	-1,546	1,145	1,823	0,177	0,213	0,023 – 2,009
SBP< 120 mmHg	1,307	0,636	4,226	0,040	3,695	1,063 – 12,846
HR >100/min	2,046	0,663	9,522	0,002	7,738	2,110 – 28,382
CRP	0,018	0,007	6,530	0,011	1,018	1,004−1,032
Glucose	-0,053	0,041	1,695	0,193	0,948	0,875 – 1,027
Constant	0,400	0,158	6,434	0,011	1,493	N/A

CI – confidence interval; AOR – adjusted odds ratio

12.3 Model C: Additional clinical and laboratory predictors with prognostic value

Model C included: age, length of hospitalization, number of comorbidities, and leukocyte count at admission.

The model was statistically significant compared with the null model ($p < 0.001$) and explained 35.6% of the variance.

Significant predictors:

Leukocytes: Leukocyte count at admission was a statistically significant predictor of mortality ($p = 0.004$). For each increase of 1 × 10^9/L, the odds of death rose by approximately 14.4% (AOR = 1.144; 95% CI: 1.044–1.253). Elevated leukocyte levels were associated with a higher risk of fatal outcome.

Number of comorbidities: A strong independent predictor ($p < 0.001$). An AOR of 1.80 (95% CI: 1.371–2.362) indicates that each additional comorbidity reduces the chance of survival by approximately 44.5%.

Non-significant predictors:

Age: A trend toward significance was observed ($p = 0.081$).

Length of hospitalization: No significant association was found ($p = 0.716$).

Table 25. *Results of the multivariable logistic regression analysis (Model C): clinical, hemodynamic, neurological, and laboratory predictors of mortality in ischemic stroke patients under 59 years of age.*

Variable	B (coefficient)	Standard error	Wald $\chi 2$	p-value	AOR [Exp(B)]	95 % CI
Age	-0,050	0,029	3,055	0,081	0,951	0,899 -1,006
Length of hospiralization (days)	0,008	0,022	0,132	0,716	1,008	0,966 – 1,052
Leukocyte count at admission	0,135	0,047	8,290	0,004	1,144	1,044- 1,253
Number of comorbidities	0,588	0,139	18,047	<0,001	1,801	1,371 – 2,362

Constant	6,196	1,687	13,480	<0,001	490,605	N/A

CI – confidence interval; AOR – adjusted odds ratio.

12.4 Model D: Final model of combined predictors with the highest independent prognostic value

The final model (Model D) integrates six variables with the strongest independent prognostic value: age, chronic left-sided heart failure (CLSHF), presence of an active infection at admission, severe neurological deficit (NIHSS >15), systolic blood pressure (SBP) ≤120 mmHg, and number of comorbidities.
The model is statistically significant ($p < 0.001$), with very good explanatory power (Nagelkerke $R^2 = 0.596$) and an overall classification accuracy of 83.9%.

Significant predictors:

SBP ≤120 mmHg: the strongest predictor of mortality (AOR = 8.510; $p < 0.001$). Hypotension at admission increases the odds of death 8.51-fold.

NIHSS >15 points: a strong predictor of mortality (AOR = 7.743; $p < 0.001$), increasing the odds of death more than 7.7-fold.

Chronic left-sided heart failure: a strong predictor of mortality (AOR = 7.600; $p < 0.001$). Patients with CLSHF have approximately 7.6-fold higher odds of death.

Non-significant variables:

Active inflammatory process at admission: a trend toward association that does not reach statistical significance in the final model (AOR = 0.331; $p = 0.087$).

Age: a tendency toward increased odds of death with advancing age, not statistically significant (AOR = 1.050; $p = 0.169$).

Number of comorbidities: a tendency toward increased odds of death with a higher comorbidity count, not statistically significant (AOR = 1.164; $p = 0.390$).

Table 26. *Results of the final multivariable logistic regression analysis (Model D): prognostic factors for mortality in ischemic stroke among patients under 59 years of age.*

Variable	B (coefficient)	Standard error	Wald	p-value	AOR [Exp(B)]	95% CI

Age	0,049	0,036	1,893	0,169	1,050	0,888-1,021
Number of comorbidities	0,152	0,177	0,739	0,390	1,164	0,608-1,215
CLSHF	2,028	0,471	18,501	<0,001	7,600	3,003-19,101
Active inflammatory process at admission	-1,106	0,646	2,937	0,087	0,331	0,093-1,172
NIHSS >15 p.	2,047	0,497	16,966	<0,001	7,743	2,924-20,507
SBP ≤120 mmHg	2,141	0,645	11,035	<0,001	8,510	2,406-30,101
Constant	1,711	1,782	0,922	0,337	5,533	N/A

CI – confidence interval; AOR – adjusted odds ratio.

V. DISCUSSION

1. Non-modifiable risk factors as predictors of mortality

The mean **age** of deceased patients was significantly higher than that of survivors. In the logistic regression models, each additional year of age increased the odds of death by 7.1% ($p < 0.05$; Models A and B). This finding is fully consistent with large cohort studies (Andersen et al., 2011; Koton et al., 2010; Kassie et al., 2019), which likewise report a progressive rise in mortality risk with advancing age.
In the final multivariable model (Model D) which included strong prognostic factors such as chronic left-sided heart failure, active infection at admission, and severe neurological deficit (NIHSS >15) age lost statistical significance ($p = 0.169$). In a younger population, this likely reflects the role of age as an indirect marker. In line with prior reports, our data suggest that, among younger patients, in-hospital mortality is driven more by the extent of brain injury than by age per se (Nedeltchev et al., 2005; Leys et al., 2002).

Regarding **sex**, no statistically significant association was observed between sex and in-hospital mortality ($\chi^2 = 0.687$, $p = 0.407$). These results accord with studies that likewise found no

independent prognostic value of sex in young patients with ischemic stroke (Andersen et al., 2011; Leys et al., 2002; Nedeltchev et al., 2005). Nevertheless, opposite findings have been reported: some authors describe a more favorable in-hospital outcome for women (OR = 0.39) among patients aged 18–45 years (Shah et al., 2025). Variability across studies is likely attributable to differences in study design, sample size and characteristics, as well as the influence of factors such as stroke severity and comorbidity profiles.

A history of **prior ischemic stroke** emerged as a significant factor in the univariate analysis, documented in 46.3% of deceased patients compared with 17.0% of survivors ($p < 0.001$). A similar association has been reported by other authors (Kassie et al., 2019). However, in our multivariable model this variable lost statistical significance ($p = 0.578$), suggesting that its effect may be partly explained by age and other comorbidities such as chronic heart failure. Patients with a history of prior stroke likely have more advanced vascular pathology and reduced functional reserve, which increases their vulnerability to a new vascular event.

In contrast to ischemic stroke, a **prior transient ischemic attack** did not show a statistically significant association with in-hospital mortality. Our findings are consistent with previous observations (Leys et al., 2002) but differ from other studies describing a protective effect, possibly related to ischemic preconditioning (Zsuga et al., 2008). The heterogeneity of published data indicates that the role of TIA as a prognostic factor in young patients remains insufficiently clarified.

A history of **prior myocardial infarction** (MI) was significantly more frequent among patients with a fatal outcome (44.8% vs 14.9% among survivors, $p < 0.001$). Univariate analysis indicated nearly a fivefold increase in the odds of death (OR = 4.649, $p < 0.001$).
Analogous to the non-modifiable factors, the prognostic effect of prior MI did not persist in the multivariable logistic regression model ($p = 0.132$). This observation is consistent with prior reports (Bhalla et al., 2008; Schneider et al., 2020) and supports the hypothesis that the impact of prior MI is mediated by other, stronger predictors included in the model.

2. Modifiable risk factors and their prognostic value

Chronic left-sided heart failure (CLSHF) emerged as one of the strongest independent predictors of in-hospital mortality. In the studied cohort, CLSHF was documented in 85.1% of deceased patients. Univariate analysis showed that the presence of CLSHF was associated with more than an elevenfold increase in the odds of death (OR = 11.23, $p < 0.001$).
This strong association persisted in multivariable regression models, where CLSHF remained statistically significant, increasing the odds of death approximately 7.6 times (AOR = 7.600, $p = 0.001$). These findings align with the broader literature identifying heart failure as an independent predictor of poor outcome (Haeusler et al., 2011; Ibeh et al., 2022). Clinically,

CLSHF carries substantial significance; its presence should prompt intensified monitoring and proactive management.

Similar results were observed for **ischemic heart disease** (IHD), which was substantially more common in the mortality group (35.8% vs 6.9%, $p < 0.001$). In univariate analysis, IHD was associated with more than a sevenfold increase in the odds of death (OR = 7.495, $p < 0.001$). However, its effect was not retained in the multivariable model ($p = 0.135$), consistent with previous studies (Schneider et al., 2020), suggesting that the prognostic relevance of IHD is mediated by other, stronger predictors.

Atrial fibrillation (AF) was more frequent among patients with a fatal outcome (9.0% vs 2.0%), but the difference did not reach statistical significance ($p > 0.05$), likely due to the small number of cases in the sample. In the univariate analysis, AF was associated with increased odds of death (OR = 4.869), again without statistical significance.
These results align with some publications (Bhalla et al., 2008; Koton et al., 2010) but differ from large studies that emphasize AF as an independent prognostic factor (Zsuga et al., 2008; Jacob et al., 2022). Our findings support the view that AF can be considered a potential predictor, given its clinical importance as a leading cause of cardioembolic stroke, which typically has a poorer prognosis.

In the present study, no statistically significant association was found between a history of **hypertension** and in-hospital mortality (OR = 0.810, $p > 0.05$). The prevalence of hypertension was extremely high and similar in the mortality group (88.1%) and among survivors (90.1%). These findings are consistent with several large studies (Andersen et al., 2011; Bhalla et al., 2008) that likewise do not identify hypertension as an independent predictor of mortality. This suggests that the influence of hypertension on early mortality may be realized indirectly, through other, stronger prognostic factors that mediate its effect.

Diabetes mellitus (DM) was significantly more frequent in the mortality group (32.8% vs 15.8% among survivors), with a statistically significant difference ($p = 0.014$). The univariate analysis confirmed a strong association, indicating that patients with DM had approximately 2.4-fold higher odds of death.
However, in the multivariable logistic regression model, DM did not retain statistical significance ($p = 0.582$). This result aligns with some reports (Schneider et al., 2020) but contrasts with large studies identifying DM as an independent predictor (Nedeltchev et al., 2005; Jacob et al., 2022). The discrepancy may reflect mediation of the DM effect by other, stronger prognostic factors included in the multivariable models, as DM was treated dichotomously (present/absent) without assessment of glycemic control.

Dyslipidemia was significantly more common among survivors (78.2% vs 59.7% in the mortality group, $p < 0.05$), suggesting a possible protective effect. This hypothesis was supported in the univariate analysis, where the presence of dyslipidemia was associated with approximately 2.6-fold higher odds of survival.
In the multivariable model, statistical significance was not reached ($p = 0.070$), although the trend toward a protective effect persisted. This observation is consistent with prior reports (Nedeltchev et al., 2005; Jacob et al., 2022). Potential explanations for this "cholesterol paradox" include protective effects of statin therapy and the phenomenon of low cholesterol as a marker of underlying systemic disease. The observed association likely reflects the impact of lipid-lowering treatment.

In the present study, **obesity** was not significantly associated with in-hospital mortality ($p = 0.199$). The proportion of patients with obesity was higher in the mortality group (9.0% vs 4.0%), but statistical significance was not reached in the univariate analysis (OR = 2.385, $p > 0.05$), likely due to the small number of cases.
These findings are consistent with other studies reporting no significant association (Jacob et al., 2022). Conversely, the literature also discusses the "obesity paradox," whereby obesity is linked to significantly lower mortality among metabolically healthy young patients (Mahadevan et al., 2024). The limited size of the obesity subgroup in our study, as well as potential mediation of the effect by other, stronger prognostic factors, likely explains the lack of statistical significance.

3.Behavioral risk factors and their relevance to mortality

In the present study, no statistically significant association was found between **smoking** and in-hospital mortality ($p = 0.467$). Smoking prevalence was similar in the mortality group (53.7%) and among survivors (59.4%), and the univariate analysis likewise did not show a significant association (OR = 1.106, $p > 0.05$). This result is consistent with most published data focusing on young patients with ischemic stroke (Leys et al., 2002; Bhalla et al., 2008; Nedeltchev et al., 2005). The lack of statistical significance despite the established role of smoking as a risk factor for stroke onset may reflect indirect long-term effects mediated through stronger prognostic factors (e.g., atherosclerosis, ischemic heart disease) or a predominant influence on stroke etiology rather than on acute-phase outcomes.

Alcohol abuse likewise showed no statistically significant association with in-hospital mortality ($p = 1.000$). Prevalence was nearly identical in the mortality group (10.4%) and among survivors (10.9%), and the univariate analysis did not demonstrate a significant association (OR = 1.042, $p > 0.05$). These findings accord with some reports (Jacob et al., 2022) but contradict others (Schneider et al., 2020). Discrepancies likely arise from differences in consumption thresholds,

the small number of patients with alcohol abuse in the present cohort, and possible mediation by stronger prognostic indicators such as severity of neurological deficit at admission. The results underscore the need for further studies with larger samples and standardized definitions.

No statistically significant association was observed between **psychoactive substance use** and in-hospital mortality ($p = 0.765$). Prevalence was similar in the mortality group (6.0%) and among survivors (7.9%), and the univariate analysis again showed no significant association (OR = 1.327, $p > 0.05$). These results are consistent with studies focusing on young stroke patients (Leys et al., 2002; Jacob et al., 2022). The lack of significance likely reflects the limited number of patients with a history of substance use and the heterogeneity of substances involved. While psychoactive substance use did not emerge as an independent predictor of mortality, it remains a recognized risk factor for stroke onset, with its principal influence likely exerted on the etiology of the vascular event rather than on acute-phase outcomes.

4.Less frequently documented modifiable risk factors as predictors of mortality

This study examined several less commonly discussed but clinically relevant factors to assess their prognostic value for in-hospital mortality in patients under 59 years of age with acute ischemic stroke.

In our analysis, an **acute inflammatory process** was significantly more frequent among patients with a fatal outcome than among survivors. In the multivariable regression model, it emerged as a strong independent predictor of in-hospital mortality, underscoring the adverse prognostic role of systemic inflammation. These observations align with reports indicating that infection or inflammation substantially increases mortality risk (Heikinheimo et al., 2013; Schneider et al., 2020). However, in the final multivariable model, the statistical significance of this factor diminished, although the trend toward an association with fatal outcome persisted. This likely reflects the inclusion of other powerful predictors that may mediate or partially overlap the effect of inflammatory processes.

With respect to **deep-vein thrombosis** (DVT), it was identified in 14.9% of patients with a fatal outcome and in 5.0% of controls. Univariate analysis showed that DVT was associated with a substantially increased probability of death (OR = 3.368), consistent with prior data (Bembenek et al., 2011). In the present study's multivariable logistic regression, however, DVT did not remain an independent predictor, a finding echoed by other research (Bembenek et al., 2012). The discrepancy between univariate and multivariable results suggests that DVT is unlikely to be a direct cause of mortality but rather a marker of more severe overall clinical status. The attenuation of the association after adjustment supports the hypothesis that stronger prognostic factors determine outcomes in this population.

In this study, a **right-to-left (R–L) shunt** was more frequent among survivors, with a statistically significant difference ($p = 0.002$), suggesting a potential protective role with respect to in-hospital mortality. These findings are consonant with a meta-analysis reporting a lower prevalence of patent foramen ovale among deceased ischemic stroke patients (Jacob et al., 2022), but they contradict other studies that found no significant association between patent foramen ovale and adverse functional outcome, including mortality (Leys et al., 2002). Divergences likely reflect differences in population characteristics and methodological approaches. Other authors report that, although an R–L shunt may not be an independent predictor of 30-day mortality, it can influence long-term, 5-year mortality (Schneider et al., 2020). Given the conflicting literature and sample limitations particularly the absence of R–L shunt cases in the mortality group the potential protective role of this factor warrants confirmation in future studies.

Malignancy was more frequent among patients with a fatal outcome (10.4%) than among survivors (5.0%). Although this difference did not reach statistical significance in our cohort, there was a trend toward an increased probability of death in the presence of cancer. A similar trend has been observed elsewhere, with significantly higher in-hospital mortality reported among patients with active malignancy (Masrur et al., 2011). Consistent with our results, Schneider et al. (2020) did not identify malignancy as an independent predictor of 30-day mortality but did highlight its importance for long-term prognosis. These findings raise questions about optimal clinical management in acute ischemic stroke with coexisting cancer, where restricted access to effective therapies (e.g., reperfusion treatment) may contribute to poorer outcomes.

In this study, **obstructive sleep apnea** (OSA) was identified only in the mortality group (3.0%) but did not emerge as an independent predictor of death (OR = 0.970). These results contrast with some reports suggesting a protective role for OSA (Festic et al., 2018). The hypothesis of "ischemic preconditioning" was not supported by our data, likely owing to the small number of OSA cases in the cohort. Conversely, other research albeit in a general-population setting supports the possibility that OSA may act synergistically to worsen stroke outcomes in individuals under 59 years of age (Vgontzas et al., 2024). The conflicting literature, together with our study's limitations, underscores the complexity of the relationship between OSA and mortality and highlights the need for future studies with larger samples of young patients.

We found that a **higher number of comorbidities** was strongly associated with increased likelihood of in-hospital death in young patients with acute ischemic stroke. The mean comorbidity count was significantly greater in the mortality group than among survivors (4.28 ± 1.66 vs 2.78 ± 1.30; $p < 0.001$). Multivariable logistic regression identified the comorbidity count as a strong independent predictor of mortality, with each additional condition reducing the chance of survival. These findings are consistent with global meta-analytic data and support the hypothesis that overall comorbidity burden rather than individual risk factors in isolation is pivotal for prognosis (Jacob et al., 2022). This may reflect complex pathophysiological

interactions that exacerbate clinical course. Multimorbidity thus emerges as a critical prognostic factor for in-hospital mortality in this population.

5.Etiologic subtypes of ischemic stroke and their prognostic role

Our analysis of etiologic subtypes showed a statistically significant overall association between subtype and in-hospital mortality ($p = 0.024$), although interpretation should be cautious due to the small sample size.

Large-artery atherosclerosis was the predominant subtype in our cohort (91.0% among deceased patients and 93.1% among survivors) and was not associated with increased odds of death (OR = 0.76, $p = 0.770$). The high frequency observed here differs from large international studies (Jacob et al., 2022; Greisenegger et al., 2011; Schneider et al., 2020), which may reflect regional patterns of risk factors in the studied population.

The cardioembolic subtype was more frequent in the mortality group than among survivors, suggesting an elevated risk of death. This finding is consistent with the literature (Jacob et al., 2022; Schneider et al., 2020), which indicates that cardioembolic strokes often present with greater clinical severity and poorer prognosis.

Lacunar stroke occurred exclusively among survivors, aligning with prior reports (Schneider et al., 2020; Jacob et al., 2022) and supporting the hypothesis that, due to its limited ischemic burden, this subtype is associated with a more favorable prognosis and lower risk of early in-hospital mortality.

Despite the potential contribution of certain etiologic subtypes (e.g., cardioembolism), the immediate prognosis appears to be primarily determined by the severity of neurological deficit at admission (Nedeltchev et al., 2005). This suggests that, in the short term, stroke severity often outweighs etiologic category in shaping outcomes. The trends observed in our study support the view that cardioembolism confers higher risk, whereas lacunar stroke is associated with a more favorable early mortality profile in patients under 59 years of age with ischemic stroke.

6.Prognostic value of neurological deficit severity and level of consciousness at admission (NIHSS and GCS)

Our analysis indicates that the severity of neurological deficit at admission, assessed by the NIHSS, is the strongest independent predictor of in-hospital mortality in patients under 59 years with acute ischemic stroke. Deceased patients presented with a significantly higher mean NIHSS score (17.07 ± 7.705) compared with survivors (7.00 ± 5.219). An NIHSS >15 points was associated with nearly ninefold higher odds of death (OR = 8.949; $p < 0.001$). In the logistic regression models, NIHSS remained the most influential factor, increasing the risk of mortality more than sevenfold ($p < 0.001$). These findings are fully consistent with the literature, which

likewise identifies a high NIHSS as a principal and independent predictor of short-term outcome, irrespective of age and sex (Schneider et al., 2020; Tejada-Meza et al., 2025; Purroy et al., 2019; Nedeltchev et al., 2005). The concordance of our results with international cohort studies supports the universal prognostic value of NIHSS for mortality in acute ischemic stroke. Assessment of neurological deficit at hospitalization should therefore be considered a key step for early identification of high-risk patients.

We also found a significant association between the level of consciousness at admission, measured by the Glasgow Coma Scale (GCS), and in-hospital mortality. Deceased patients had a substantially lower mean GCS (10.01 points) than survivors (13.95 points), in line with other studies confirming GCS as an important prognostic indicator (Szczudlik et al., 2000; Koton et al., 2010). However, in the multivariable model, GCS ≤12 points did not reach statistical significance ($p = 0.177$). This is likely explained by the strong correlation between GCS and NIHSS, with the latter providing a more granular characterization of neurological impairment and emerging as the more powerful independent predictor. While GCS is valuable for rapid initial assessment, our data indicate that the broader scope of NIHSS underpins its superior independent prognostic value.

7.Prognostic significance of vital signs

Analysis of systolic blood pressure (SBP) at admission revealed a U-shaped association with in-hospital mortality. The relationship was most pronounced for low SBP (<120 mmHg), which was linked to increased odds of death; the multivariable logistic model confirmed its independent effect, with hypotension raising the odds of mortality more than eightfold (AOR = 8.510). Elevated SBP (≥180 mmHg) was more frequent among deceased patients but did not reach statistical significance as an independent predictor ($p = 0.274$). These findings suggest that, in the acute phase of ischemic stroke, hypotension bears a stronger association with early mortality than hypertension. The observed U-shaped pattern aligns with prior reports (Bangalore et al., 2017). Low SBP may reflect severe systemic pathology or hemodynamic instability leading to impaired cerebral perfusion and exacerbation of ischemic injury, whereas elevated SBP in the acute phase may represent a compensatory mechanism to sustain perfusion in affected brain regions.

Admission heart rate (HR) likewise differed significantly between survivors and non-survivors. Mean HR was higher in the mortality group (90.28 beats/min) than in controls (75.06 beats/min). When categorized, tachycardia (>100 beats/min) occurred substantially more often among deceased patients, and the χ^2 test confirmed a strong association with fatal outcome ($p < 0.001$). Univariate and multivariable logistic analyses showed that HR above 100 beats/min increased the odds of death more than sevenfold (AOR = 7.738; $p = 0.002$), establishing tachycardia as a robust independent predictor of adverse prognosis in acute ischemic stroke. These results are

consistent with larger cohort studies (Erdur et al., 2014; Han et al., 2020; Kuo et al., 2021) demonstrating a dose-dependent relationship between higher HR and unfavorable clinical outcomes. Elevated HR at admission likely reflects the intensity of the systemic response to ischemic injury, supporting its inclusion in routine risk-assessment models for young and middle-aged patients.

8.Prognostic value of neuroimaging findings

In this analysis, the mean ASPECTS was lower among patients with a fatal outcome (7.09 ± 1.774) than among survivors (7.93 ± 1.265). Despite this difference, statistical testing did not show a significant association between ASPECTS and in-hospital mortality. The estimated odds ratio (OR = 1.63) indicates that patients with ASPECTS ≤7 had 1.63-fold higher odds of death, but this association did not reach statistical significance. These findings differ from much of the published literature argely based on older cohorts where lower ASPECTS is a strong predictor of mortality (Barber et al., 2000; Yoo et al., 2014; Haussen et al., 2016). A likely explanation is the age structure of the present cohort: younger age may be protective, attenuating the adverse impact of extensive infarction reflected by low ASPECTS (Li et al., 2025). Overall, the data suggest that younger age modifies the effect of ischemic lesion burden on in-hospital mortality.

No statistically significant association was detected between stroke localization and in-hospital mortality ($p = 0.291$). There was a trend toward lower odds of death with anterior-circulation involvement (OR = 0.713) and toward higher mortality with right-sided lesions, but these did not reach statistical significance ($p = 0.053$). This contrasts with several key reports highlighting the prognostic value of topographic classification (Purroy et al., 2019; Nedeltchev et al., 2005; Koton et al., 2010). The heterogeneity of published data, together with our focus on a younger population, underscores the need for larger studies to clarify the independent prognostic value of localization in this age group.

In the present study, the presence of a hyperdense middle cerebral artery (MCA) was not significantly associated with in-hospital mortality ($\chi^2 = 0.839$, $p = 0.360$). Nonetheless, the odds-ratio analysis suggested a trend toward increased risk (OR = 1.493), consistent with clinical reasoning. These findings contrast with the prevailing literature, which identifies a hyperdense MCA as a strong, independent predictor of poor outcome due to malignant cerebral edema (Wijdicks et al., 2014). The discrepancy likely reflects the specific age group studied here: stroke in younger adults often has distinct etiologies and pathophysiology, potentially leading to a lower frequency of massive territorial infarcts and, consequently, a weaker prognostic contribution of the hyperdense MCA sign. Prior work also indicates that this marker may lose independent prognostic value in multivariable models when other imaging features already indicate large infarct burden (Fiorelli et al., 2000). Larger, youth-focused cohorts are needed to validate the prognostic value of the hyperdense MCA sign in this population.

9.Laboratory markers at admission as predictors of mortality

Our results clearly show that admission C-reactive protein (CRP) levels are a significant predictor of in-hospital mortality. Mean CRP values were substantially higher in the mortality group (51.56 mg/L) compared with survivors (11.01 mg/L). The Mann–Whitney test confirmed this statistically significant difference ($p < 0.001$), and logistic regression indicated that each 1 mg/L increase in CRP reduces the chance of survival by 1.8% (OR = 1.118; $p = 0.011$). These findings are consistent with multiple authoritative studies establishing CRP as an important early biomarker (Bian et al., 2023; Yu et al., 2019; Idicula et al., 2009). Elevated levels reflect the systemic inflammatory response, a key prognostic factor in the pathophysiology of stroke. Limitations include the lack of a standardized threshold for "high" CRP in the literature and the need for differential diagnosis given possible concomitant infectious conditions. Despite these challenges, our results strongly support CRP as a reliable and readily available biomarker for mortality prediction in acute ischemic stroke, useful for early identification of high-risk patients requiring intensified monitoring.

According to our results, elevated leukocyte counts at the start of hospitalization are significantly associated with mortality in the acute phase of stroke. The mean leukocyte count in the mortality group (12.39 × 10^9/L) was significantly higher than in controls (9.88 × 10^9/L), with a statistically significant difference ($p = 0.012$). Logistic regression confirmed that with each 1 × 10^9/L increase, the odds of death rose by 14.4% (AOR = 1.144; $p = 0.004$). These observations accord with global data supporting leukocytosis as a marker of poor prognosis. Several studies have identified elevated white blood cell count as a significant independent predictor of 30-day mortality (Schneider et al., 2020; Furlan et al., 2014). Other authors also emphasize the role of leukocytes in stroke pathogenesis, with higher counts associated with endothelial dysfunction, hypercoagulability, and thrombogenesis (Zia et al., 2012).

Nevertheless, contradictory data exist. Some studies have not confirmed leukocytosis as an independent predictor of mortality in multivariable models, concluding that while strongly linked to stroke severity, it does not remain independent after adjustment (Szczudlik et al., 2000; Kammersgaard et al., 1999). This suggests leukocytosis may primarily reflect the extent of brain injury. Particularly relevant to our cohort, Heikinheimo et al. (2015) studied young patients and found that elevated leukocyte count was associated with unfavorable functional outcome but not mortality. Discrepancies likely stem from methodological differences (age ranges, sampling times, control for concurrent infections). Our results support leukocytosis at admission as an important prognostic marker of in-hospital mortality in young ischemic stroke patients. Although some literature indicates dependence on stroke severity, our logistic regression demonstrates independent prognostic value, underscoring the utility of this readily available laboratory parameter in early risk stratification.

Our findings show that admission serum glucose levels were significantly higher in the mortality group (9.65 mmol/L) than among survivors (7.56 mmol/L). This difference was statistically significant in the univariate analysis ($p < 0.001$), supporting the hypothesis that hyperglycemia adversely affects outcomes in the acute phase of ischemic stroke. This observation is consistent with multiple authoritative studies. For example, each 1 mmol/L increase in glucose has been associated with a 42.0% increase in the odds of death (OR = 1.42; $p < 0.001$) (Zsuga et al., 2008). Similar associations have been reported elsewhere (Szczudlik et al., 2000; Koton et al., 2010), underscoring a broad consensus on the negative prognostic impact of hyperglycemia. However, in our multivariable logistic regression model, serum glucose did not emerge as an independent predictor of mortality ($p = 0.193$). This aligns with reports suggesting that persistent hyperglycemia, rather than a single measurement, is the stronger predictor (Yong, Kaste, 2008). In our cohort, admission hyperglycemia may correlate with other, stronger predictors included in the model. These results highlight the complexity of glucose's prognostic role and point to the need for dynamic monitoring of glucose levels in the acute phase particularly in younger patients—to refine risk assessment.

In our study, no statistically significant difference in admission serum sodium was found between the mortality and survivor groups ($p = 0.261$). Although mean values were similar, the mortality group exhibited a wider range (109 to 169 mmol/L), suggesting severe homeostatic disturbances in a subset of these patients. These results contrast with some key literature emphasizing the prognostic importance of electrolyte abnormalities. A strong statistical association has been reported between sodium measurements in the first six hours and mortality (OR = 6.89) (Fofi et al., 2012), and admission hyponatremia has been linked to increased mortality (Rodrigues et al., 2014). The discrepancy with published findings (e.g., Fofi et al., 2012) may reflect methodological differences: their work focused on extremes (hypo- and hypernatremia), whereas our primary analysis examined mean values. The wide spread observed in our mortality group suggests that not the mean but the extreme deviations may be the true prognostic drivers. Pathophysiology supports this view: hyponatremia contributes to cerebral edema, while hypernatremia often indicates severe neurological compromise.
Overall, our analysis suggests that extreme deviations in sodium balance may have prognostic value, underscoring the need for a more granular approach that evaluates hypo- and hypernatremia as distinct risk factors.

10.Additional prognostic factors: length of hospitalization and administered treatment

Our study identified a statistically significant difference in length of hospital stay between deceased patients and survivors ($p < 0.001$). Mean stay was substantially longer among survivors, whereas deaths in the target group occurred earlier after admission. However, in the multivariable logistic regression model, no significant association was observed between length

of hospitalization and mortality (p = 0.716). This discrepancy is expected and accords with prior work indicating that length of stay is not a prognostic factor per se but rather a reflection of clinical outcome (Lin, Lin, Yeh, 2022; Lu et al., 2025). Our data support the view that shorter stays among non-survivors primarily reflect severe initial status and early death, whereas prolonged hospitalization among survivors stems from the need for extended management of neurological deficits and complications. The lack of significance in the multivariable model confirms that length of stay is an indicator of disease course rather than an independent predictor.

In our cohort, no statistically significant relationship was found between intravenous thrombolysis and in-hospital mortality in patients under 59 years of age with ischemic stroke (p = 0.805; OR = 1.161). These findings are consistent with other research that did not identify thrombolysis as a significant predictor of 30-day mortality in young patients (Schneider et al., 2020). By contrast, they differ from the large SITS-ISTR study, in which younger patients aged 18 to 50 years exhibited markedly lower mortality than older patients (4.9% vs 14.4%) (Toni et al., 2012). These results should be interpreted with caution: a key limitation of our study is the small proportion of patients treated with thrombolysis (6.0% in the mortality group and 6.9% in controls), which reduces the reliability of statistical inferences on treatment efficacy and precludes firm conclusions.

VI. CONCLUSION

The present dissertation study focuses on the analysis of prognostic factors associated with in-hospital mortality in patients aged 18–59 years with acute ischemic stroke. The investigation encompasses a broad spectrum of non-modifiable, modifiable, and less frequently documented risk factors, as well as key clinical, imaging, and laboratory parameters.

The results of the analysis indicate that low systolic blood pressure (≤120 mmHg), the severity of neurological deficit (NIHSS >15 points), and chronic left-sided heart failure emerge as the most significant and independent predictors of fatal outcome. These three parameters demonstrate consistent prognostic value across all multivariate models, underscoring the critical role of severe neurological impairment, hemodynamic instability, and pronounced cardiac dysfunction in determining in-hospital mortality within this population.

Factors such as C-reactive protein (CRP), leukocyte count, and elevated heart rate (>100 bpm) exhibited strong prognostic significance in intermediate models but were excluded from the final model (Model D) to prevent multicollinearity and overfitting. Their effect is considered to be strongly mediated by the more powerful and independent clinical predictors included in Model D (such as active infection, NIHSS >15, SBP ≤120 mmHg, and chronic left-sided heart failure).

This suggests that their prognostic value is indirect and largely driven by their association with the primary mechanisms underlying fatal outcomes.

Other variables, including age, acute inflammatory response, and the number of comorbidities, demonstrated “mixed” significance across different models and lost their statistical strength in the final model. This further supports the hypothesis of a partially mediated influence through the dominant predictors.

Another group of factors, such as prior vascular events (stroke, myocardial infarction), comorbid conditions like diabetes mellitus, decreased level of consciousness, and duration of hospitalization, lost statistical significance in the multivariate analysis, indicating that their effect is secondary and determined by stronger clinical and hemodynamic variables.

The study did not find a significant association between in-hospital mortality and factors such as sex, arterial hypertension, behavioral risk factors, neuroimaging findings, serum sodium levels at admission, or type of treatment administered, suggesting that their impact is limited or indirect in the examined population.

In conclusion, the present dissertation provides empirical evidence contributing to a deeper understanding of prognosis in young and middle-aged patients with ischemic stroke. The results highlight that accurate prediction of fatal outcomes requires not only the identification of individual risk factors but also the evaluation of their complex interactions, an approach essential for improving clinical practice and enabling timely identification of high-risk patients.

VII. SUMMARY OF FINDINGS

The present study aims to identify and evaluate prognostic factors for in-hospital mortality among young and middle-aged patients with ischemic stroke.

The main conclusions of the dissertation are as follows:

1. The severity of neurological deficit (NIHSS >15 points), chronic left-sided heart failure, and low systolic blood pressure (≤120 mmHg) are the most powerful and independent predictors of fatal outcome.
2. Certain factors demonstrate prognostic value in individual models but lose their significance after the inclusion of stronger predictors. These include age, acute inflammatory response, elevated heart rate, increased CRP levels, leukocyte count, and the number of comorbidities.

3. Factors such as previous vascular events, some comorbid conditions (ischemic heart disease, diabetes mellitus, dyslipidemia, deep vein thrombosis, malignancy), decreased level of consciousness, and length of hospitalization lose statistical significance in the multivariate analysis, indicating that their effects are mediated by stronger clinical variables.
4. Variables such as sex, arterial hypertension, atrial fibrillation, obesity, obstructive sleep apnea, behavioral risk factors, imaging indicators (ASPECTS, hyperdense middle cerebral artery sign, vascular localization), and serum sodium levels do not show a statistically significant association with in-hospital mortality in the studied population.
5. A comprehensive risk assessment at admission, integrating both acute and background clinical parameters, is essential for the early identification of high-risk patients and for optimizing therapeutic strategies.

VIII. CONTRIBUTIONS

1.Contributions of original character

The present dissertation provides the following original contributions:

1. **Specific analysis of a young and middle-aged cohort.**
   This work includes a detailed descriptive and comparative analysis of the demographic, clinical, and imaging characteristics of patients aged 18–59 years. The analysis enables a more precise identification of age-specific factors with potential relevance for improving prognostic assessment in this population.
2. **Identification of independent prognostic factors.**
   By applying multivariate logistic regression analysis, the study identifies independent risk factors associated with in-hospital mortality. This statistical approach allows for the distinction of variables with a direct and autonomous impact on fatal outcomes, providing a solid basis for future clinical investigations.
3. **Comprehensive analysis of prognostic markers.**
   The study integrates and evaluates the impact of a wide range of potential prognostic factors, including clinical indicators (such as NIHSS score and vital parameters), neuroimaging findings (lesion localization, ASPECTS score), laboratory parameters (inflammatory and metabolic markers), and etiological subtypes (TOAST classification). The integrated analysis of these variables offers an in-depth understanding of the complex interactions between different mechanisms contributing to fatal outcomes.

2. Confirmatory contributions

This study confirms and extends existing evidence in the literature, validating it for a specific population of young and middle-aged patients with ischemic stroke. The main confirmatory contributions are:

Chronic left-sided heart failure (CLSHF) as a powerful independent predictor of mortality.
Our results clearly show that CLSHF is among the strongest independent prognostic factors for fatal outcome, underscoring the critical role of cardiac status in acute stroke prognosis.

NIHSS as a principal predictor of mortality due to ischemic stroke.
We robustly demonstrate that admission NIHSS reflecting the severity of neurological deficit is the strongest independent prognostic factor for death, confirming its universal value in a younger age group as well.

Prognostic value of hemodynamic parameters.
We found that low systolic blood pressure (≤120 mmHg) and tachycardia (≥100/min) are independent predictors of mortality.

Prognostic value of laboratory markers.
We found that elevated CRP and increased leukocyte count are independent predictors of death from ischemic stroke. These readily available indicators have practical value for early risk stratification.

These contributions deepen understanding of prognosis in this specific population and provide concrete data that can be used to improve clinical practice.

IX. LIMITATIONS OF THE STUDY

This study has several methodological limitations that should be considered when interpreting the findings:

Small sample size. The limited cohort particularly within subgroups characterized by less common risk factors such as psychoactive substance use, alcohol misuse, obstructive sleep apnea, right-to-left shunt, and malignancy may have reduced the statistical power. This likely contributed to the absence of significant associations for these factors, even though larger studies have identified them as prognostically relevant.

Retrospective design. As a retrospective analysis, the study relies on existing medical records. Incomplete documentation or missing data for certain variables may have influenced the results or constrained in-depth analysis of specific factors.

Restricted geographic scope. Data were collected from a single center, which limits the generalizability of the findings to broader populations at the national or international level.

Focus on in-hospital mortality. The study addresses only mortality occurring during hospitalization, which does not capture long-term outcomes. Factors that are not predictive of early mortality may nonetheless have substantial impact on long-term survival and functional recovery.

X. Publications Related to the Dissertation

Tsalta-Mladenov M, **Nikolay P**, Georgieva D, Andonova S. Influence of the COVID-19 pandemic on acute stroke care. Experience of a comprehensive stroke center in Bulgaria. Neurology Asia. 2021; 26(1): 9-13.

Nikolay P, Georgieva D. Comparative prognostic value of the NIHSS and Glasgow coma scale for in-hospital mortality in patients under 60 years with acute ischemic stroke. Scripta Scientifica Medica. 2025; Online first

XI. APPENDICES

Appendix 1: National Institutes of Health Stroke Scale (NIHSS)

National Institute of Health Stroke Scale – NIHSS	
1a. Level of consciousness (quantitative impairment)	0: Alert, appropriate 1: Somnolent 2: Stuporous 3: Responds only with reflex motor or autonomic activity, or is completely unresponsive (coma)
1b. Questions for assessment of impaired level of consciousness	0 – Answers both questions correctly. 1 – Answers one question correctly. 2 – Answers neither question correctly. (What is the current month? What is his/her age?)
1c. Commands for assessment of impaired level of consciousness	0 – Performs both commands correctly. 1 – Performs one command correctly. 2 – Performs neither command correctly. (Open and close the eyes. Squeeze and release the non-paretic hand.)
2.Best gaze (ocular movements/gaze palsy)	0 – Normal ocular movements. 1 – Partial gaze palsy. 2 – Conjugate eye deviation or total gaze palsy.

3. Visual fields / visual deficits	0 – No visual loss. 1 – Partial hemianopia. 2 – Complete hemianopia. 3 – Bilateral hemianopia (cortical blindness).
4. Facial palsy — lesion of the seventh cranial nerve (CN VII)	0 — Normal, symmetric facial movements. 1 — Mild paresis. 2 — Partial paresis. 3 — Severe (total) paralysis of one or both sides.
5. Motor function (ARM) 5a - Left arm 5b - Right arm	0 — No drift for 10 seconds or more. 1 — Holds the limb up to 10 seconds without touching the bed. 2 — Cannot maintain position; drifts down to the bed. 3 — No effort against gravity; the limb falls. 4 — No movement. 9 — Amputation or joint contracture.
6. Motor function (LEG) 6a - Left leg 6b - Right leg	0 — No drift for 10 seconds or more. 1 — Holds the limb up to 10 seconds without touching the bed. 2 — Cannot maintain position; drifts down to the bed. 3 — No effort against gravity; the limb falls. 4 — No movement. 9 — Amputation or joint contracture.
6. Limb ataxia	0 — No ataxia. 1 — Ataxia in one limb. 2 — Ataxia in two limbs.
7. Sensory	0 — Normal sensation. 1 — Mild to moderate sensory loss. 2 — Severe or total sensory loss.
8. Best language	0 — No aphasia. 1 — Mild to moderate aphasia. 2 — Severe aphasia. 3 — Mutism or global aphasia.

9. Dysarthria	0 — Normal articulation. 1 — Mild to moderate dysarthria. 2 — Severe dysarthria
10. Extinction and inattention	0 — No abnormality. 1 — Visual, tactile, auditory, spatial, or personal (somatic) inattention. 2 — Profound hemi-inattention or neglect affecting more than one sensory modality
Total NIHSS score (0–42 points)	

Appendix 2: Glasgow Coma Scale (GCS)

Glasgow Coma Scale		
SYMPTOMS	SCORE	DATE AND TIME OF ASSESSMENT
EYE OPENING Spontaneous To speech To pain No response	 4 3 2 1	
VERBAL RESPONSE Oriented Confused Inappropriate words Incomprehensible sounds No response	 5 4 3 2	

	1	
MOTOR RESPONSE Obeys commands Localizes pain Withdraws from pain Abnormal flexion (decorticate) Abnormal extension (decerebrate) No response	6 5 4 3 2 1	
Total:		

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