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GLYCEMIA IN ACUTE ISCHEMIC STROKE – PROGNOSTIC SIGNIFICANCE AND ASSOCIATION WITH METABOLIC AND INFLAMMATORY MARKERS

THESIS SUMMARY
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The dissertation contains 143 standard pages and is illustrated with 38 tables, 28 figures and 4 schemes. The bibliography contains 285 titles, of which 9 in Cyrillic and 276 in Latin. The dissertation work was discussed and directed for public defense at a meeting of the Department Council at the Second Department of Internal Medicine, Medical University "Prof. Dr. Paraskev Stoyanov" - Varna.

The public defense of the dissertation will take place on 07.05.2025 at ……. at an open meeting of the Scientific Jury. The defense materials are available in the Library of the Medical University "Prof. Dr. Paraskev Stoyanov" - Varna, 55 Marin Drinov Str. and on the University's website (mu-varna.bg).

Note: In the thesis summary, the numbers of the tables and figures do not correspond to the numbers in the dissertation.

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Abbreviations used in the text

admBG	blood glucose on admission
AH	arterial hypertension
AIS	acute ischemic stroke
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
avBG	average blood glucose
Baso	basophils
BG	blood glucose
CBC	complete blood count
CGM	continuous glucose monitoring
COPD	chronic obstructive pulmonary disease
CV	coefficient of variation
CV 1-4	coefficient of variation from day 1 to day 4 of hospitalization
CV 2-4	coefficient of variation from day 2 to day 4 of hospitalization
CRP	C-reactive protein
DBC	differential blood count
DBP	diastolic blood pressure
DICND	Department for Intensive Care of Nervous Diseases
DTACS	Department for Treatment of Acute Cerebral Strokes
DM	diabetes mellitus
Eo	eosinophils
Er	erythrocytes
GG	glycemic gap
GV	glycemic variability
Hb	hemoglobin
HbA1c	glycated hemoglobin
Hct	hematocrit
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
IHD	ischemic heart disease
LDL-C	low-density lipoprotein cholesterol
Leu	leukocyte
Lympho	lymphocytes
Mono	monocytes
mRS	modified Rankin Scale
mSHR	modified stress hyperglycemia ratio

ndT2DM	newly diagnosed type 2 diabetes mellitus
Neutro	neutrophils
NG	normoglycemia
NIHSS	National Institutes of Health Stroke Scale
NIHSS 1	stroke severity at hospital admission
NIHSS 2	stroke severity at discharge
PGRN	progranulin
Plt	platelets
PVD	peripheral vascular disease
RFs	risk factors
SBP	systolic blood pressure
SD	standard deviation
SH	stress hyperglycemia
SHR	stress hyperglycemia ratio
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglycerides
TNF-α	tumor necrosis factor alpha

I. INTRODUCTION

Cerebrovascular disease occupies a major place among socially significant diseases due to the high morbidity, mortality and severe disability observed in connection with acute cerebrovascular accident. Ischemic strokes are the leading cause of mortality and long-term disability worldwide, and Bulgaria ranks second in the world in terms of morbidity and mortality from stroke.

Glycemic control is of utmost importance for patients with acute ischemic stroke (AIS). Maintaining glucose levels within certain limits plays an important role both in the course of stroke and in its clinical and functional outcome.

Plasma glucose levels have a high degree of instability and are affected by many and varied factors – energy intake and expenditure, hormonal changes, accompanying diseases, medication intake, etc. Any type of stress for the body can lead to a sharp increase in glucose levels. This gives grounds for defining the term "stress hyperglycemia" (SH). In general, it refers to a sudden increase in blood glucose (BG) levels from the usual in connection with the acute condition. Precisely because background glycemia is important for detecting patients presenting with SH, absolute BG levels appear insufficiently reliable for this purpose. In this regard, the use of glycated hemoglobin (HbA1c) based glycemic variables is introduced, which are highly hoped that, taking into account the usual BG levels, they will more accurately differentiate patients with true SH from those with poorly controlled diabetes mellitus (DM), for example.

Acute ischemic stroke, as an acute illness that puts the body in a state of stress, is often accompanied by SH, which can affect its course and outcome. However, whether it simply reflects the greater degree of stroke severity or is a direct cause of adverse outcomes is still a matter of debate. At the same time, hypoglycemia is extremely dangerous for ischemia-damaged brain tissue and represents a serious challenge in attempts to therapeutically control elevated glucose levels. In addition, the high variability in glucose levels also seems to have a detrimental effect. Given these considerations, strict glucose monitoring is crucial for patients with acute stroke in order to timely detect and correct deviations in glucose concentrations.

Given that it is a stress hormone, cortisol appears to be a potential marker that would provide insight into the strength of the stress response in acute stroke and thus help differentiate cases of SH. However, the available evidence for a direct neurotoxic effect of elevated cortisol levels raises the question of whether cortisol is simply a reflection of stroke severity or is independently associated with adverse outcome in these patients.

Of interest is the serum marker progranulin (PGRN), which although mainly

associated with neurodegenerative diseases, literature data indicate that it could be used to assess the severity and prognosis of acute stroke. Moreover, more recent sources consider the marker to be an adipokine and associate it with insulin resistance and possibly with the pathogenesis of type 2 diabetes mellitus (T2DM). It is extremely curious to compare its levels in patients with AIS and different glycemic status.

Blood glucose, as a modifiable risk factor for stroke that can be therapeutically influenced, requires us to know the impact of abnormal glucose levels, the consequences they are associated with, and the prognostic power they carry. The detection of laboratory parameters associated with BG would be useful in determining the patient's risk profile, assessing the mortality risk, as well as in deciding on therapeutic behavior. Last but not least, identifying different biomarkers with predictive value in acute stroke would be beneficial to more accurately assess the prognosis of these patients, which is important to improve treatment and reduce disability rates.

II. AIM AND TASKS

Aim:

To look for a relationship between glycemia level and outcome in patients with AIS, as well as an association with metabolic and inflammatory markers.

Tasks:

- To assess the level of glycemia in hospitalized patients with AIS with and without T2DM using indicators of absolute and relative glycemia and glycemic variability (GV).
- To conduct a comparative characteristic of some clinical, glycemic, metabolic and inflammatory parameters between groups with different glycemic status, different severity of AIS and outcome from hospitalization.
- To investigate the association of AIS severity and hospitalization outcome with some clinical, glycemic, metabolic and inflammatory parameters.
- To examine the relationship between glycemic parameters and some metabolic and inflammatory markers.
- To assess whether HbA1c-based glycemic variables are better determinants of stress response compared to the absolute value of BG at hospitalization and to evaluate their prognostic value.

III. MATERIALS AND METHODS

1. Study participants

Stage I. Retrospective study of a cohort of patients hospitalized for AIS in the Second Clinic for Nervous Diseases with DICND and DTACS of the University Hospital "St. Marina", Varna, for the period of May 2016 to April 2017.

Inclusion criteria – consecutively hospitalized patients with AIS; age over 18 years.

Exclusion criteria – type 1 diabetes mellitus.

From the electronic patient registration system of the University Hospital "St. Marina", Varna, we extracted data on age, severity of AIS at admission assessed by the National Institutes of Health Stroke Scale (NIHSS) (Table 1), clinical outcome (survivor or deceased), as well as some results of routinely performed laboratory parameters – admission BG (admBG), hematocrit (Hct) and leukocyte (Leu) values, lipid profile indicators and creatinine.

Table 1. National Institutes of Health Stroke Scale

NIHSS score	Stroke severity
0	No stroke symptoms
1–4	Minor stroke
5–15	Moderate stroke
16–20	Moderate to severe stroke
21–42	Severe stroke

Stage II. Cross-sectional study of patients hospitalized for AIS in the Second Clinic for Nervous Diseases with DICND and DTACS of the University Hospital "St. Marina", Varna, for the period of June 2021 to May 2023, selected in the first 24 hours of hospitalization. All patients included in the study had a negative result from a rapid antigen test for Covid-19.

Inclusion criteria:

- Signed informed consent;
- Men and women with AIS - history and clinic of AIS less than 24 hours from the onset of symptoms; CT/MRI brain imaging within 12 hours of admission;
- Age over 18 years.

Exclusion criteria:

- Type 1 diabetes mellitus**;**

- Chronic administration of corticosteroids;
- Anemic syndrome, Hb<90 g/L;
- Hemotransfusion performed in the previous 3 months;
- End-stage renal failure (eGFR <15 ml/min/1.73m2);
- Pregnancy or lactation.

2. Clinical methods (valid for stage II)

2.1. Part of the clinical data was taken from the medical history – age, comorbidities and risk factors (RFs) for AIS, physical examination data and neurological status, severity of AIS according to NIHSS at admission (NIHSS 1) and at discharge (NIHSS 2), hospital stay, clinical outcome (survivor, deceased).

2.2. Anamnesis based on data from the patient, relatives and/or available medical documentation regarding the presence of diabetes, its duration, ongoing therapy, as well as anthropometric data of known height and weight, with a view to an approximate estimation of body mass index.

2.3. Assessment of the degree of disability after AIS (functional outcome) at discharge using the modified Rankin Scale (mRS) **(Table 2)**.

Table 2. Modified Rankin Scale (mRS)

Score	Description
0	No symptoms
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk and attend to bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

2.4. As outcome measures, we determined the severity of AIS at discharge (NIHSS 2), clinical outcome (survivor or deceased), functional outcome at discharge (mRS), and length of hospital stay.

3. Laboratory methods (valid for stage II)

3.1. Part of the laboratory data was taken from the medical history – parameters included in the standard tests when admitting a patient with AIS in an emergency setting – complete blood count (CBC), admBG, lipid profile, urea, creatinine, liver enzymes, C-reactive protein (CRP).

3.2. Within 24 hours of hospitalization, regardless of the time of day, a blood sample was taken for HbA1c, cortisol, insulin (in patients not receiving insulin or sulfonylurea treatment), PGRN and tumor necrosis factor alpha (TNF-α) testing. The latter two parameters were included subsequently in the study and therefore were not examined in all patients.

3.3. The laboratory analysis of the studied parameters was conducted in the Central Clinical Laboratory of the University Hospital "St. Marina", Varna.

- HbA1c (%) – turbidimetric inhibition immunoassay (TINIA) for hemolyzed whole blood (Cobas e 601, ROCHE). Determination of HbA1c was standardized according to the DCCT/NGSP protocol;
- Cortisol (nmol/l) – chemiluminescent immunoassay with non-isotopic labeling of antibodies (ADVIA Centaur CP, Siemens);
- Insulin (mU/l) – electrochemiluminescence immunoassay (ECLIA) (Cobas e 601, ROCHE);
- Progranulin (Human Progranulin/PGRN) – ELISA (enzyme-linked immunosorbent assays) with a ready-made test kit (Novus Biologicals, Bio-Techne). The tests are performed according to the protocol requirements of the manufacturer. The method measures the level of PGRN in serum, plasma and other body fluids. Serum PGRN levels were reported in ng/ml.
- Tumor necrosis factor alfa (Human TNF-α) – ELISA with a ready-made test kit (R and D Systems, Bio-Techne). The tests are performed according to the protocol requirements of the manufacturer. The method measures the level of TNF-α in serum, plasma, cell supernatants. Serum TNF-α levels were reported in pg/ml.

3.4. Examination of fasting capillary BG on 3 consecutive days after the day of hospitalization with a glucometer (Free Style Optium Neo, Abbot) to study inter-day GV. Based on these measurements, the average fasting blood glucose level (avBG) and coefficient of variation (CV) from day 2 to day 4 (CV 2-4) were calculated, and taking into account the admBG, the CV from day 1 to day 4 (CV 1-4) was calculated, as well as the difference between the maximum and minimum BG values (ΔBG).

3.5. Calculation of HbA1c-based glycemic variables as indicators of SH.
ADAG (A1c-derived average glucose) (mmol/L) = (1.59 x HbA1c (%)) - 2.59.

- Stress hyperglycemia ratio (SHR) = admBG (mmol/L) / ADAG (mmol/L)
- Modified SHR (mSHR) = admBG (mmol/L) / HbA1c (%)
- Glycemic gap (GG) (mmol/L) = admBG (mmol/L) – ADAG (mmol/L)

3.6. Calculation of Neutro/Lympho ratio

3.7. Calculation of PGRN/TNF-α ratio

4. Statistical methods

Data were processed with GraphPad Prism 7.03 (for Stage I) and 8.3.0 (for Stage II) for Windows, IBM SPSS Statistics 26 was used for some of the analyses. For all performed analyses an acceptable level of significance was $p < 0.05$ with a confidence interval of 95%.

Descriptive statistics: quantitative variables were described with mean (standard deviation) or median (interquartile range), in some cases with minimum and maximum values; qualitative variables were described with n (number of observations) and relative frequency of distribution (in percentages); Kolmogorov-Smirnov and Shapiro-Wilk tests to check the normality of the distribution.

Hypothesis testing methods: Student's t-test for comparing means from two independent samples with a normal distribution and Mann-Whitney test when there is no normal distribution; chi-square ($\chi 2$) test for comparing proportions; one-way analysis of variance (one-way ANOVA) for comparing means from independent samples in more than two groups with a normal distribution (Sheffe's posthoc test) and Kruskal-Wallis test when there is no normal distribution (Mann-Whitney posthoc tests with Bonferroni correction).

Correlation analysis to assess the strength of the relationship between two variables: Pearson's correlation coefficient (r) for interval or proportional variables, with a normal distribution, and Spearman's rank correlation coefficient (r_s) for ordinal variables and when the distribution is not normal.

Multiple regression analysis to consider the influence of independent variables on a given dependent variable.

ROC analysis to calculate sensitivity and specificity of a given indicator.

IV. RESULTS

1. Stage I of the study

The retrospective study included a cohort of 555 patients with AIS aged 25 to 98 years (mean age 73.21±11.0 years) with a similar proportion of males and females (48.47% vs. 51.53%, p=0.31). According to the level of admBG and the presence of T2DM, we divided the patients into 3 groups (Fig. 1) – with NG (without known DM with admBG < 7.8 mmol/L), with SH (without known DM with admBG ≥ 7.8 mmol/L) and with T2DM (with known DM or with admBG ≥ 11.1 mmol/L).

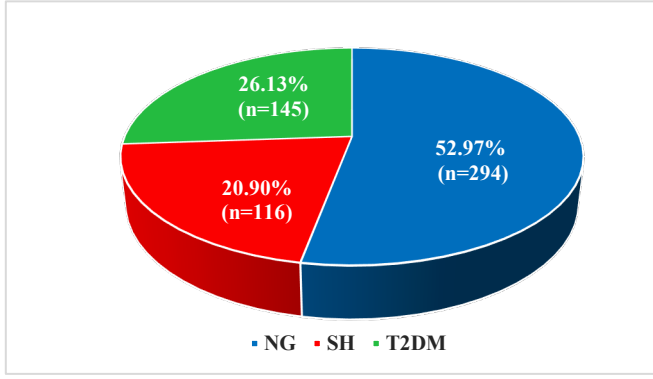


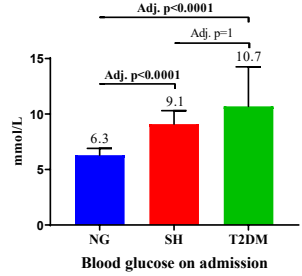
Fig. 1. Distribution of patients according to the level of admBG and the presence of DM

1.1. Main characteristics of patients in the individual groups

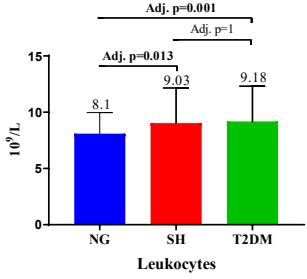
We evaluated some basic clinical and laboratory parameters that would be related to glycemic status in AIS (Table 3). As expected, we observed a significant difference between the groups in terms of admBG ($p<0.0001$), considering that this is the main indicator for their differentiation. Subsequent posthoc analysis demonstrated that admBG was significantly lower in the NG group compared to those with SH and T2DM (Fig. 2 A). Additionally, we found significant differences regarding the values of leukocytes ($p=0.0003$) and creatinine ($p=0.003$), which also showed significantly lower levels in the NG group compared to the other two groups (Fig. 2 B, C).

Table 3. Comparative characteristics of the evaluated clinical and laboratory parameters

Parameters \ Groups	NG (n=294)	SH (n=116)	T2DM (n=145)	F/H, p value
Age (years), median (IQR)	74 (66–83)	76 (67–82)	74 (66.5–79.5)	H=1.231 p=0.745
Males, n (%)	143 (48.64)	57 (49.14)	69 (47.59)	F=0.035, p=0.966
admBG(mmol/L), median (IQR)	6.3 (5.7–6.9)	9.1 (8.05–14.25)	10.7 (8.3–10.3)	**H=328.7 p<0.0001**
Leu (10^9/l), median (IQR)	8.1 (6.33–9.96)	9.03 (7.42–12.15)	9.18 (7.06–12.32)	**H=16.51 p=0.0003**
Hct (L/L), median (IQR)	0.392 (0.356–0.429)	0.401 (0.364–0.436)	0.399 (0.364–0.439)	H=2.576 p=0.276
TC (mmol/L), median (IQR)	4.75 (4.07–5.51)	4.71 (3.92–5.59)	4.74 (3.7–5.83)	H=0.013 p=0.994
LDL-C (mmol/L), median (IQR)	2.8 (2.25–3.52)	2.8 (2.04–3.6)	2.79 (1.88–3.58)	H=0.917 p=0.632
HDL-C (mmol/L), median (IQR)	1.2 (1.0–1.46)	1.17 (0.95–1.49)	1.12 (0.88–1.38)	H=5.068 p=0.08
Creatinine (µmol/L), median (IQR)	80 (67–99)	88 (74–108)	89 (73–113)	**H=11.55 p=0.003**



A)



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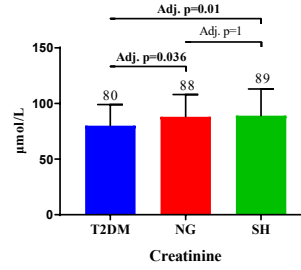


C)

Fig 2. Comparative analysis of admBG (A), leukocytes (B) and creatinine (C) between groups

1.2. Assessment of the severity of AIS

We assessed the severity of AIS in surviving patients (n=412) and found that the proportion of moderate AIS (5-15 points) was significantly higher than that of other stroke severity grades (vs.: 1-4 points, p<0.0001; 16-20 points, p<0.0001; 21-42 points, p<0.0001) and was observed in over half of the cases of non-fatal AIS (57.11%) (Fig. 3).

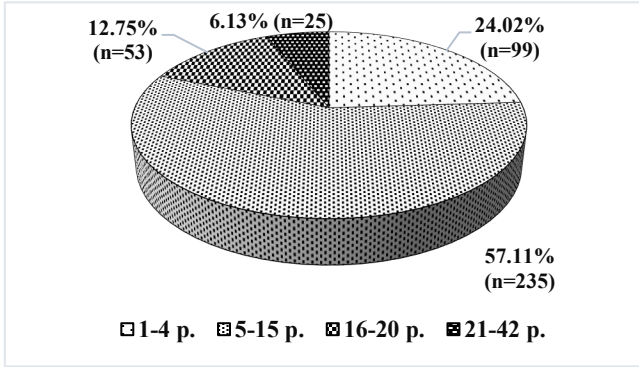


Fig. 3. Distribution according to severity of AIS in survivors

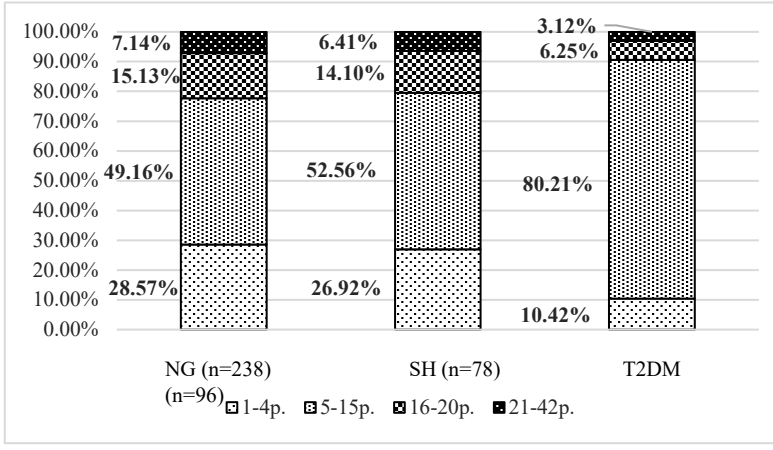


Fig 4. Distribution of AIS severity levels in survivors according to glycemic status

We further analyzed the prevalence of different AIS severity levels in surviving patients according to glycemic status (Fig. 4). We found that in the group with T2DM, the proportion of patients with moderate AIS (NIHSS 5-15 points) was significantly higher compared to that in the other two groups (vs.: NG, p<0.0001; SH, p=0.0001), at the expense of significantly smaller proportions of mild AIS (NIHSS 1-4 points) (vs.: NG, p=0.0004; SH, p=0.005) and moderate to severe and severe AIS combined (NIHSS 16-42 y) (vs.: NG, p=0.006; SH, p=0.038).

1.3. BG on admission according to the severity of AIS

We established a statistically significant difference in the level of admBG between groups (p=0.016) with different stroke severity. The level of admBG was significantly higher in moderate non-fatal AIS compared to mild AIS, but we did not find further increase in SH with the severity of stroke (Fig. 5).

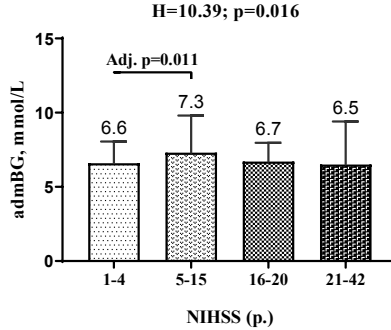


Fig 5. Comparative analysis of admBG according to severity of AIS

1.4. Prevalence of fatal outcome and parameters according to the outcome of AIS

A fatal endpoint was found in 25.77% (n=143) of the patients in the study. From the distribution according to the glycemic status (Fig. 6), it is noticeable that the proportions of the SH and T2DM groups are greater at the expense of those with NG among the deceased patients compared to the distribution of groups in the general cohort (Fig. 1). The differences are more obvious when directly comparing the proportions of survivors and deceased between groups with different glycemic status (Fig.7). We observed a significant difference in the prevalence of fatal outcome between SH and NG groups (p=0.003), as well as

T2DM and NG groups (p=0.001), but not between SH and T2DM groups (p=0.86).

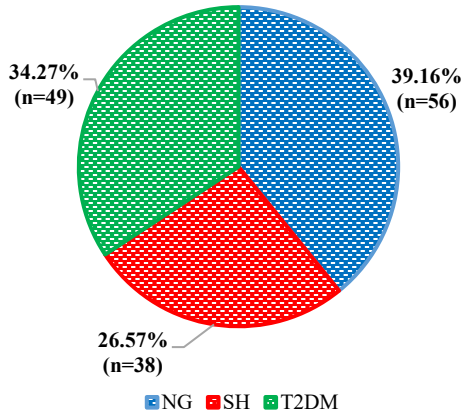


Fig. 6. Distribution of deceased patients according to glycemic status

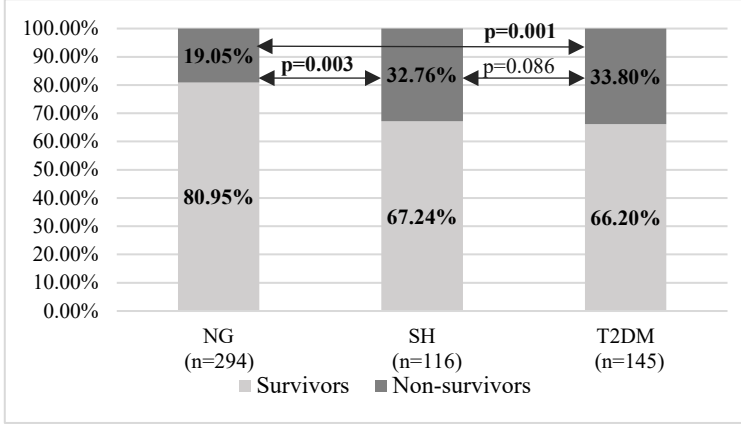


Fig. 7. Prevalence of fatal outcome in the groups with NG, SH and T2DM

We compared the characteristics of patients with a fatal and a favorable outcome (Table 4) and found that deceased patients were significantly older than those who survived (p<0.0001) and demonstrated significantly higher values of admBG (p=0.0001), leukocyte count (p=0.027) and creatinine (p=0.035). At the same time, they showed significantly lower levels of total cholesterol (p=0.001)

and LDL-C (p=0.001). We did not observe differences in hematocrit and HDL-C levels.

Table 4. Comparative characteristics of patients with fatal and favorable outcome

Parameters \ Groups	Survivors (n=412)	Non-survivors (n=143)	U, p value
Age (years), median (IQR)	73 (65–80)	79 (72–85)	**U=19634, p<0.0001**
admBG (mmol/L), median (IQR)	7.0 (5.9–8.94)	7.9 (6.69–10.3)	**U=23080, p=0.0001**
Leu (109/l), median (IQR)	8.34 (6.74–10.42)	9.49 (6.93–12.83)	**U=14777, p=0.027**
Hct (L/L), median (IQR)	0.396 (0.363–0.432)	0.395 (0.354–0.445)	U=28767, p=0.768
TC (mmol/L), median (IQR)	4.8 (4.12–5.67)	4.42 (3.41–5.4)	**U=17844, p=0.001**
LDL-C (mmol/L), median (IQR)	2.88 (2.26–3.6)	2.61 (1.85–3.3)	**U=19015, p=0.001**
HDL-C (mmol/L), median (IQR)	1.18 (0.99–1.45)	1.16 (0.89–1.43)	U=19159, p=0.293
Creatinine (μmol/L), median (IQR)	84 (68–100)	87 (74–116.8)	**U=25723, p=0.035**

We examined the differences in the parameters where there was a significant difference between survivors and deceased patients, in the groups with different glycemic status. A significantly older age of deceased patients compared to survivors was confirmed for all three groups (NG, U=3872, p<0.0001; SH, U=1025, p=0.009; T2DM, U=1658, p=0.003). The tendency for lower levels of total cholesterol and LDL-C in patients with a fatal outcome was present in all three groups, but statistical significance was observed for total cholesterol in the groups with NG (U=3957, p=0.023) and SH (U=548.5, p=0.002), and for LDL-C – only in the SH group (U=694.5, p=0.003). Regarding admBG, leukocyte count and creatinine, we did not find any intergroup differences.

1.5. Correlation analysis of admBG, severity of non-fatal AIS and fatal outcome with the assessed clinical and laboratory parameters

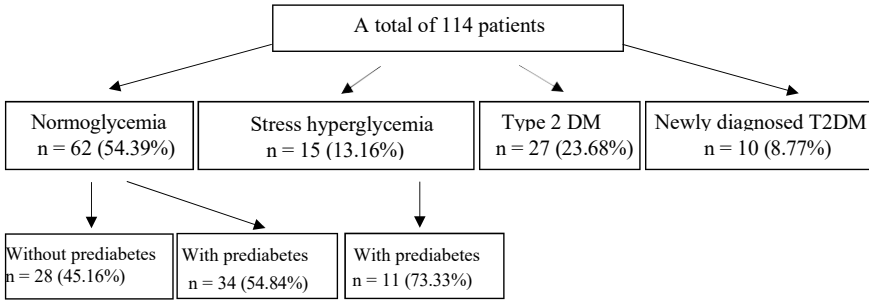
We observed a weak positive association of admBG with hematocrit (r=0.086; p=0.043), as well as with leukocyte count (r=0.121; p=0.007). In addition, we found a weak negative relationship of admBG with patients' age (r=(-0.085); p=0.046) and with HDL-C level (r=(-0.14); p=0.002). Correlation analysis of the severity of non-fatal AIS showed a weak positive association with patients' age (r=0.14; p=0.004), as well as with leukocyte count (r=0.111; p=0.026). The severity of non-fatal AIS was weakly negatively correlated with HDL-C level (r=(-0.121); p=0.019). A positive association with weak strength was found between lethal outcome on the one hand and patients' age (r=.256; p<0.0001), leukocyte count (r=0.156; p=0.001) and creatinine level (r=0.125;

p=0.003) on the other. Moreover, we reported a weak negative relationship with the fatal outcome of total (r=(-0.156); p=0.0004) and LDL-C (r=(-0.151); p=0.001) (Table 5).

Table 5. Correlation analysis of admBG, severity of non-fatal AIS and fatal outcome with clinical and biochemical parameters

	admBG	NIHSS	Fatal outcome
Age	**r=(–0.085); p=0.046**	**r=0.14; p=0.004**	**r=0.256; p<0.0001**
Leu	**r=0.121; p=0.007**	**r=0.111; p=0.026**	**r=0.156; p=0.001**
Hct	**r=0.086; p=0.043**	r=(–0.095); p=0.055	r=(–0.026); p=0.535
admBG	**---**	r=0.079; p=0.111	r=0.075; p=0.075
TC	r=0.071; p=0.107	r=0.002; p=0.963	**r=(–0.156); p=0.0004**
LDL-C	r=0.023; p=0.612	r=0.041; p=0.424	**r=(–0.151); p=0.001**
HDL-C	**r=(–0.14); p=0.002**	**r=(–0.121); p=0.019**	r=(–0.02); p=0.652
Creatinine	r=0.076; p=0.075	r=(–0.044); p=0.377	**r=0.125; p=0.003**

2. Stage II of the study



Scheme 1. Distribution of patients by groups according to glycemic status

The cross-sectional study included a cohort of 114 patients with AIS aged 43 to 93 years (mean age 73.23±11.15 years), with a comparable proportion of males (n=54; 47.37%) and females (n=60; 52.63%) (p=0.43). They were divided into 4 groups, according to the level of admBG and the presence of DM considering the value of HbA1c – with NG (without known DM with admBG < 7.8 mmol/L and HbA1c < 6.5%), with SH (without known DM with admBG ≥ 7.8 mmol/L and HbA1c < 6.5%), with known T2DM and with newly diagnosed

T2DM (ndT2DM) (with HbA1c ≥ 6.5%) (Scheme 1, Fig. 8).

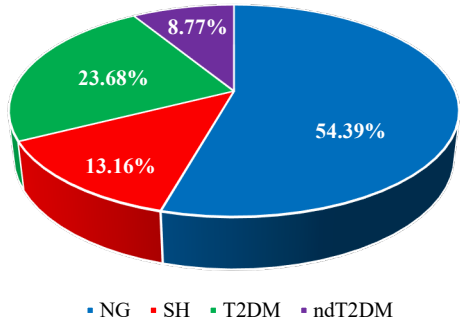


Fig. 8. Prevalence (%) of NG, SH, T2DM and ndT2DM

Based on HbA1c values between 5.7% and 6.4%, we identified a significant proportion of patients with prediabetes in the NG (54.84%) and SH (73.33%) groups. Only 24.56% (n=28/114) of all patients with AIS had no deviations in glycemic status. According to the HbA1c level in patients with known T2DM, we determined the proportion of those with good (HbA1c < 7.0%, n=11, 44%) and, respectively, poor control of DM (HbA1c > 7.0%, n=14, 56%). According to some researchers, in patients with well-controlled DM, an admBG value > 7.8 mmol/l can also be used for SH. We reported this in 45.45% (n=5) of patients with T2DM and HbA1c < 7.0%. Hypoglycemic events were observed in three patients, all from the T2DM group – two with good control of diabetes and one with poor control. A fatal outcome was recorded in one of these patients from the well-controlled DM group. Due to the low frequency of hypoglycemic events, they were not further analyzed.

2.1. Main characteristics of patients according to glycemic status

We observed a significant difference in gender distribution (p=0.027) between groups with different glycemic status, with a predominance of females in the groups with SH and T2DM, with a significantly smaller proportion of affected males in the SH group compared to those with NG (p=0.016) and with ndT2DM (p=0.014) (Fig. 9).

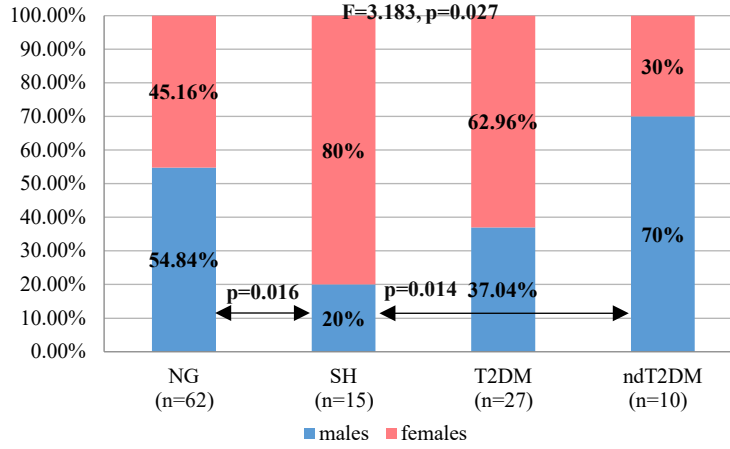


Fig. 9. Comparative analysis of gender distribution between groups

There was no difference in the mean age of patients in the groups according to glycemic status (p=0.487). The age distribution by decade in the total cohort (Table 6) shows that the age group between 70-89 years is the most affected, with 67.55% of the participants falling into this age category. We observed a significantly greater proportion of patients ≥ 70 years of age (n=80/114, 70.18%) compared to their proportion under this age (n=34/114, 29.82%) (p<0.0001).

Table 6. Age distribution of patients

Age (years)	NG (n)	SH (n)	T2DM (n)	ndT2DM (n)	Total (n, %)
40–49	4	0	1	0	5 (4.38)
50–59	4	0	3	1	8 (7.02)
60–69	13	1	4	3	21 (18.42)
70–79	19	9	14	2	44 (38.6)
80–89	20	5	4	4	33 (28.95)
90–99	2	0	1	0	3 (2.63)
All	62	15	27	10	114 (100)

We also analyzed the gender distribution by decade and found that with increasing age, the proportion of affected females progressively increases at the expense of males. We reported that at age < 70 years, there were significantly more men with AIS (n=22/34, 64.71%) than women (n=12/34, 35.29%) (p=0.016) and vice versa at age ≥ 70 years, there was a significant predominance of women (men, n=32/80, 40%; women, n=48/80, 60%) (p=0.012) (Table 7).

Table 7. Gender distribution of patients by age group

Age (years)	Males (n, %)	Females (n, %)	Total (n)
40–49	4 (80)	1 (20)	5
50–59	5 (62.5)	3 (37.5)	8
60–69	13 (61.9)	8 (38.1)	21
70–79	18 (40.91)	26 (59.09)	44
80–89	13 (39.39)	20 (60.61)	33
90–99	1 (33.33)	2 (66.67)	3
All	54	60	114

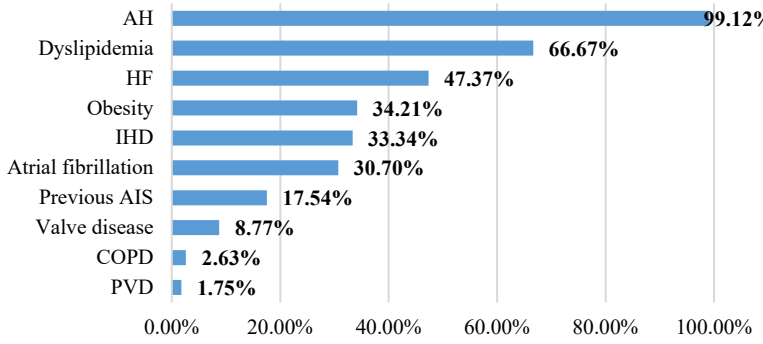


Fig. 10. Frequency of comorbidities in the total cohort

The assessed comorbidities were precisely the RFs for AIS, in addition to the presence of diabetes. No significant difference was found in their prevalence in the groups with different glycemic status (arterial hypertension, AH, p=0.844; dyslipidemia, p=0.824; atrial fibrillation, p=0.769; valvular disease, p=0.066; ischemic heart disease, IHD, p=0.338; chronic obstructive pulmonary disease, COPD, p=0.835; peripheral vascular disease, PVD, p=0.416; previous AIS, p=0.227; obesity, p=0.105) with the exception of heart failure (HF) (F=2.794, p=0.044). It was significantly more prevalent in the group with SH (80%) compared to the other groups. We analyzed the frequency of RFs for AIS in the general cohort (Fig. 10). We found that almost all of the studied patients had concomitant AH, dyslipidemia was present in more than 2/3, nearly half of the patients had concomitant HF, and about 1/3 had obesity, IHD, or atrial fibrillation. The following were less common: previous AIS (17.54%), valvular disease (8.77%), COPD (2.63%), and PVD (1.75%).

2.2. Parameters of severity and outcome of AIS according to glycemic status (Talbe 8)

Table 8. Parameters of severity and outcome of AIS by groups according to glycemic status

Grous / Parameters	NG (n=62)	SH (n=15)	T2DM (n=27)	ndT2DM (n=10)	F/H, p value
NIHSS 1 (т.), mean (SD)	10.63±6.12	15.33±8.39	11.33±6.51	8.7±5.21	**F=2.69 p=0.0497**
NIHSS 2 (т.), median (IQR)	6 (3–10.25)	5 (1.75–14.75)	5 (3–8)	3.5 (3–4.75)	H=1.6 p=0.66
mRS (т.), median (IQR)	3 (1–4)	6 (3–6)	3 (1–5)	1 (1–5)	H=7.312 p=0.063
Fatal outcome, n (%)	12 (19.35)	8 (53.33)	6 (22.22)	2 (20)	**F=2.693 p=0.0496**
Hospital stay (days), median (IQR)	5 (4.0–8.25)	8 (4–13)	5 (4–7)	5 (4–10)	H=1.454 p=0.693

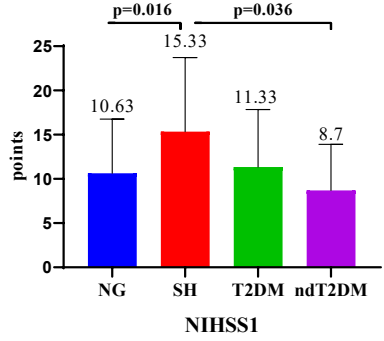


Fig. 11. Comparative analysis of AIS severity at admission between groups

We observed a significant difference between the groups regarding the severity of AIS at admission (p=0.0497), and it was significantly greater in the group with SH compared to those with NG and ndT2DM (Fig. 11). The distribution of the severity of AIS between the groups with different glycemic status (Fig. 12) showed that in patients with SH, a significantly smaller proportion of moderate AIS (NIHSS 5-15p.) was observed (compared to: NG, $\chi 2=5.655$, p=0.017; T2DM, $\chi 2=4.869$, p=0.027; ndT2DM, $\chi 2=6.48$, p=0.011), as well as a

significantly larger proportion of moderate to severe and severe AIS (NIHSS 16-42p.) (compared to: NG, $\chi 2=7.969$, $p=0.005$; T2DM, $\chi 2=5.852$, $p=0.016$; ndT2DM, $\chi 2=6.0$, $p=0.014$).

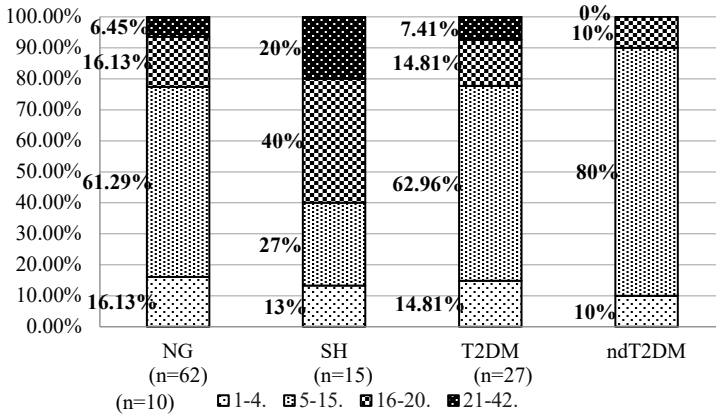


Fig. 12. Distribution of patients by severity of AIS in groups with different glycemic status

Borderline significance was observed in terms of functional outcome ($p=0.063$), with the median again highest in the group with SH. And although without significance, the longest hospital stay is also noticeable in the group with SH (Table 8).

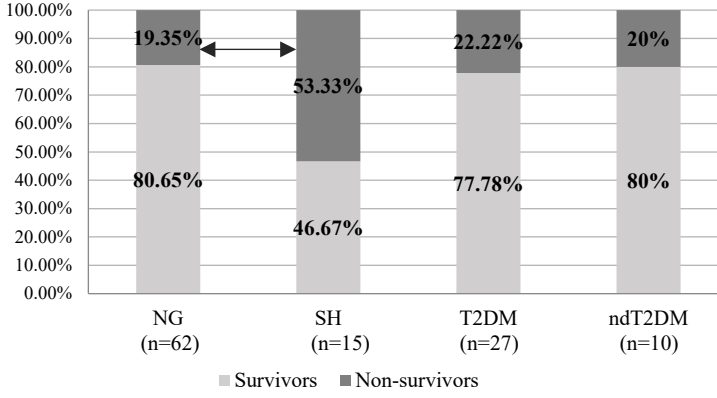


Fig. 13. Distribution according to the outcome of AIS in the groups with different glycemic status

Additionally, we found a significant difference in the incidence of fatal outcome between the groups with different glycemic status (p=0.0496) (Table 8), and this difference was again at the expense of the group with SH. With over half of the patients in the group affected, the proportion of deceased patients with SH was significantly higher than those in the groups with NG (p=0.008) and T2DM (p=0.043) (Fig. 13).

Similar to the age distribution by decade in the general cohort, we recorded the highest mortality among people aged 70-89 years (Table 9), with a significantly higher proportion of patients with a fatal outcome aged ≥ 70 years (n=24/28, 85.71%) compared to those < 70 years (n=4/28, 14.29%) (p<0.0001).

Table 9. Age distribution of deceased patients

Age (years)	NG (n)	SH (n)	T2DM (n)	ndT2DM (n)	Total (n, %)
40–49	0	0	0	0	0 (0)
50–59	0	0	0	0	0 (0)
60–69	4	0	0	0	4 (14.29)
70–79	3	3	5	0	11 (39.28)
80–89	5	5	0	2	12 (42.86)
90–99	0	0	1	0	1 (3.57)
All	12	8	6	2	28 (100)

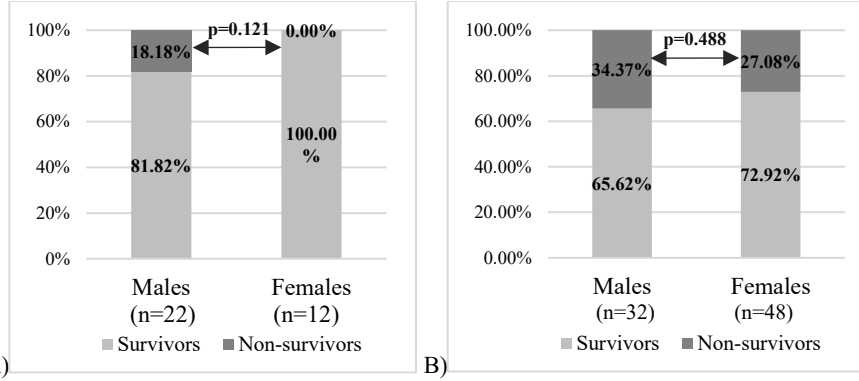


Fig. 14. Distribution according to outcome of AIS in males and females <70 years of age (A) and ≥70 years of age (B)

The analysis of the gender distribution of deceased patients (n=28) did not show gender differences, although there was a slight male predominance (males, n=15, 53.57%; females, n=13, 46.43%; p=0.59). In addition, we examined mortality in both sexes separately in the age group under and over 70 years (Fig. 14 A, B), finding no significant difference between the proportion of deceased males compared to that of deceased females in any of the two age groups (< 70 years – males, n=4/22, 18.18%; females, n=0/12, 0%; p=0.121; ≥ 70 years – males, n=11/32, 34.37%; women, n=13/48, 27.08%; p=0.488).

2.3. Laboratory parameters according to glycemic status

2.3.1. Main laboratory parameters in patients with AIS according to glycemic status

Regarding the CBC indicators, in contrast to the I stage of the study, where we observed a reliable difference in the level of leukocytes, in the II stage this was not confirmed (p=0.128), although we reported higher values in the leukocyte count in the group with SH. However, we found significant differences in the level of neutrophils (p=0.001), which were significantly higher in the group with SH compared to those with NG and T2DM (Fig. 15 A). Although the lymphocyte level was significantly lower in the group with SH compared to the other groups, a significant difference was not registered (p=0.118). On the other hand, the Neutro/Lympho ratio showed a significant difference between the groups with different glycemic status (p=0.003), as its level was significantly higher in the group with SH compared to that with NG (Fig. 15 B). From the standard biochemical tests, we observed a significant difference in the level of ASAT (p=0.010), and again, we recorded the highest values in the group with SH, reliably exceeding those in T2DM (Fig. 15 C). Similar to neutrophils and the Neutro/Lympho ratio, the inflammatory marker CRP also showed significant differences in its value between groups (p = 0.029) with the highest levels in the SH group significantly exceeding those in the NG control group (Fig. 15 D). Regarding the lipid profile indicators, we found significant differences between the groups in terms of HDL-C (p=0.0002) and TG (p=0.012) levels. Subgroup analysis (Fig. 15 E) reported significantly higher HDL-C levels in the NG and SH groups compared to those with known and newly diagnosed T2DM. With respect to TG, in contrast to HDL-C, the values were higher in the groups with known and newly diagnosed T2DM compared to those with NG and SH, with the differences being significant in the group with known T2DM compared to that with NG (Fig. 15 F).

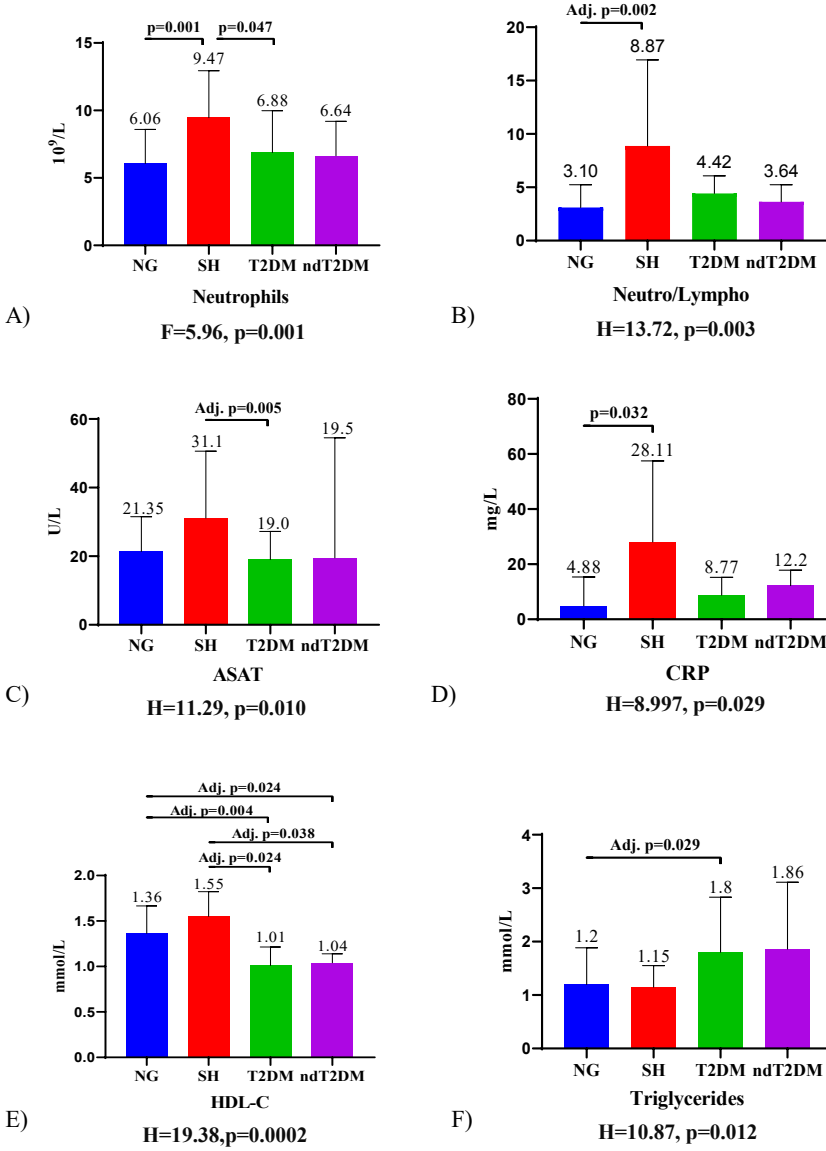


Fig. 15. Comparative analysis of the value of neutrophils (A), Neutro/Lympho ratio (B), ASAT (C), CRP (D), HDL-C (E) and triglycerides (F), between the groups

2.3.2. Glycemic and hormonal parameters according to glycemic status (Table 10)

Table 10. Comparative characteristics of the studied glycemic and hormonal parameters

Groups / Parameters	NG (n=62)	SH (n=15)	T2DM (n=27)	ndT2DM (n=10)	F/H, p value
admBG (mmol/L), median (IQR)	6.23 (5.7–6.9)	8.4 (7.9–9.9)	9.4 (7.2–13.4)	8.35 (5.32–19.55)	**H=43.43, p<0.0001**
BG2 (mmol/L), mean (SD)	6.15±1.32	6.72±1.53	9.49±4.31	10.03±5.06	**F=12.041, p<0.0001**
BG3 (mmol/L), mean (SD)	5.88±1.31	6.25±1.46	9.45±2.79	8.72±2.33	**F=22.948, p<0.0001**
BG4 (mmol/L), mean (SD)	5.72±0.92	5.93±0.67	8.63±2.84	8.51±2.24	**F=17.442, p<0.0001**
avBG (mmol/L), mean (SD)	5.98±1.03	6.7±1.29	9.28±2.74	9.01±2.97	**F=24.588, p<0.0001**
CV 1–4 (%), median (IQR)	9.99 (6.75–15.66)	22.87 (16.66–30.54)	24.25 (12.01–39.09)	16.89 (13.91–33.77)	**H=31.17, p<0.0001**
CV 2–4 (%), median (IQR)	8.2 (5.02–13.76)	9.42 (6.06–17.95)	14.8 (7.77–23.35)	10.51 (6.02–16.47)	**H=9.0, p=0.029**
ΔBG (mmol/L), median (IQR)	1.2 (0.8–2.0)	3.2 (2.24–4.65)	4.22 (2.2–8.5)	2.9 (2.17–11.23)	**H=43.1, p<0.0001**
HbA1c (%), median (IQR)	5.74 (5.32–5.99)	6 (5.55–6.13)	7.21 (6.26–8.92)	7.1 (6.83–10.61)	**H=49.13, p<0.0001**
SHR, median (IQR)	0.96 (0.87–1.05)	1.31 (1.14–1.4)	0.95 (0.8–1.28)	0.96 (0.65–1.28)	**H=20.77, p=0.0001**
mSHR, median (IQR)	1.1 (0.99–1.18)	1.46 (1.33–1.65)	1.2 (0.98–1.67)	1.18 (0.79–1.77)	**H=24.56, p<0.0001**
GG (mmol/L), median (IQR)	(–0.26) ((–0.82)–0.3)	1.89 (1.0–2.95)	(–0.48) ((–2.2)–2.97)	(–0.31) ((–2.82)–4.72)	**H=18.58, p=0.0003**
Cortisol (nmol/L), mean (SD)	701.7±380.8	1039±668	630.7±305.1	615.9±271.6	**F=3.761, p=0.013**
Insulin (μIU/mL), median (IQR)	9.48 (5.12–21.45)	13.8 (9.6–19.1)	10 (7.92–14.55)	15.55 (10.08–22.28)	H=3.5, p=0.321

As expected, glycemic parameters demonstrated significant differences between groups and admBG values, capillary BG measured in the morning in the fasting state on the following three days of hospitalization (BG2, BG3, BG4), fasting avBG, glucose variability parameters, and also HbA1c apparently dominated in the T2DM group. Interestingly, HbA1c-based glycemic variables showed another pattern, namely the highest levels in the group with SH.

On admission, the level of BG in the group with NG, rightly considered as control, showed significantly lower levels compared to the other three groups (Fig. 16).

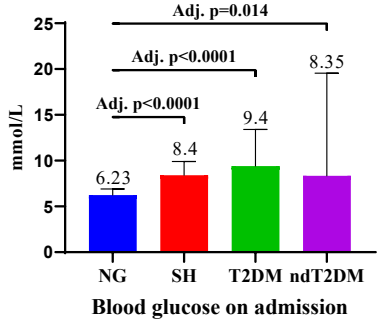


Fig. 16. Comparative analysis of the value of admBG between the groups

Figure 17 shows the dynamics of BG levels in the first four days of hospitalization in the different groups.

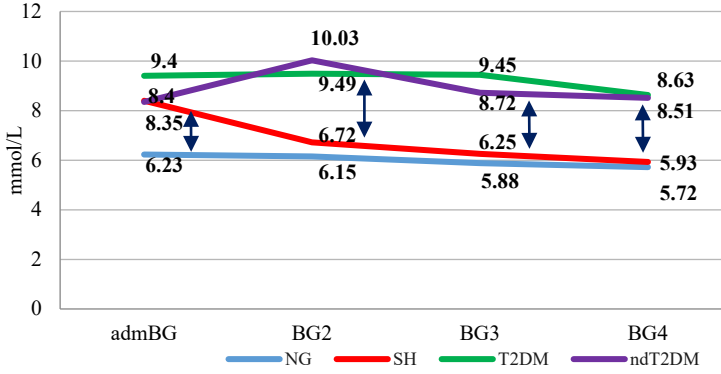


Fig. 17. Dynamics of BG levels in different groups

The changes in BG levels in the group with SH were extremely indicative. There we observed increased values of admBG similar to those in the groups with T2DM (Adj. p=1) and ndT2DM (Adj. p=0.779), but significantly higher than its values in the group with NG (Adj. p<0.0001). In the following days, only in the CH group we reported a drop in БG levels to levels similar to those in the NG group(BG2, p=0.927; BG3, p=0.931; BG4, p=0.988), but significantly lower than BG in the T2DM (BG2, p=0.035; BG3, p<0.0001; BG4, p=0.002) and ndT2DM

groups (BG2, p=0.048; BG3, p=0.025; BG4, p=0.037). This dynamic is reflected in the parameter CV 1-4 days of hospitalization, where not only the groups with diabetes, but also the group with SH demonstrated significantly greater variability in BG levels compared to the group with NG (Fig. 18 A). Similarly, the difference between the maximum and minimum measured BG values was significantly greater in the DM and SH groups compared to the NG group (Fig. 18C). Leaving aside the day of hospital admission associated with the greatest stress, we observed a significantly greater GV only in the group with known T2DM compared to that with NG (Fig. 18 B).

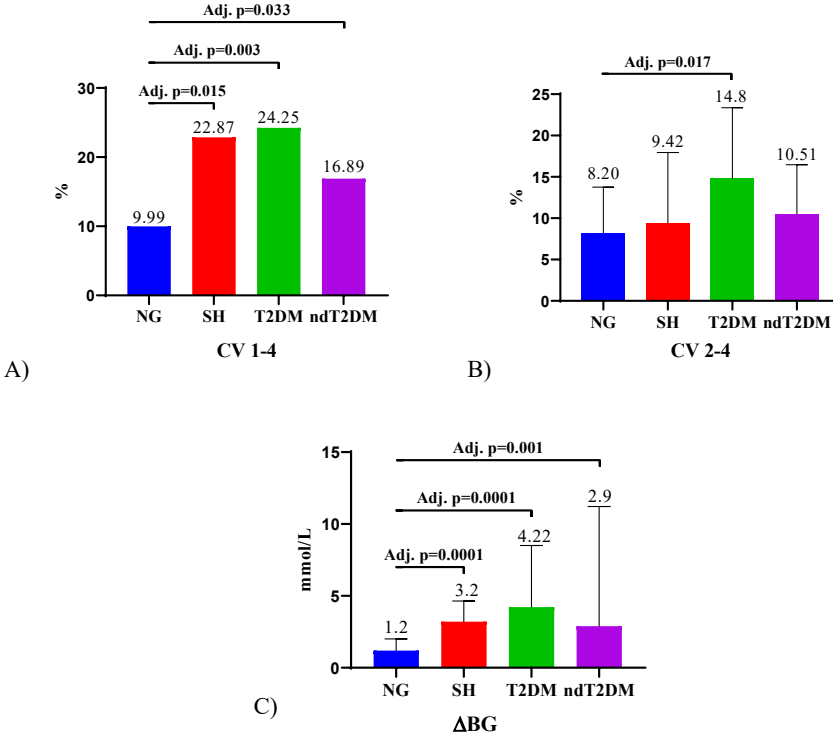
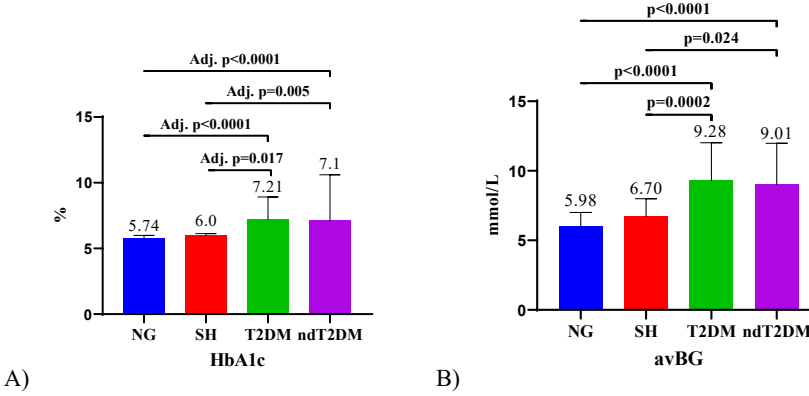


Fig. 18. Comparative analysis of the values of CV 1-4 (A), CV 2-4 (B) and ΔBG (C) between the groups

Logically, given that it is a marker for diagnosis and control of the disease, HbA1c showed significantly higher values in the groups with known and newly diagnosed T2DM compared to those without (Fig. 19 A). Similar to the average value of BG for the last three months in the face of HbA1c, the level of fasting avBG during hospitalization showed a similar trend, namely significantly higher values in the groups with known and newly diagnosed T2DM compared to those without diabetes (Fig. 19 B).



A) B)

Fig. 19. Comparative analysis of HbA1c (A) and avBG (B) values between groups

Of particular interest were our observations regarding HbA1c-based glycemic variables, all of which showed significant differences between groups (SHR, p=0.0001; mSHR, p<0.0001; GG, p=0.0003). As markers of acute stress hyperglycemia, similar to the severity of AIS at admission, they demonstrated significantly higher levels precisely in the SH group compared to the other groups (Fig. 20 A, B, C).

As for serum cortisol, we also found significant differences in its levels between the individual groups (p=0.013). As a stress hormone, similar to the glycemic variables and the severity of AIS at admission, its values were significantly higher in the SH group compared to the control group with NG and that with T2DM (Fig. 20D). We found no significant differences in insulin levels between groups with different glycemic status (p=0.321).

We checked whether there was a gender difference in our patients with regard to glycemic and hormonal parameters and observed only significantly higher cortisol levels in women compared to men (males 632.9±320.9, females 803.4±484.7, t=2.183, p=0.031).

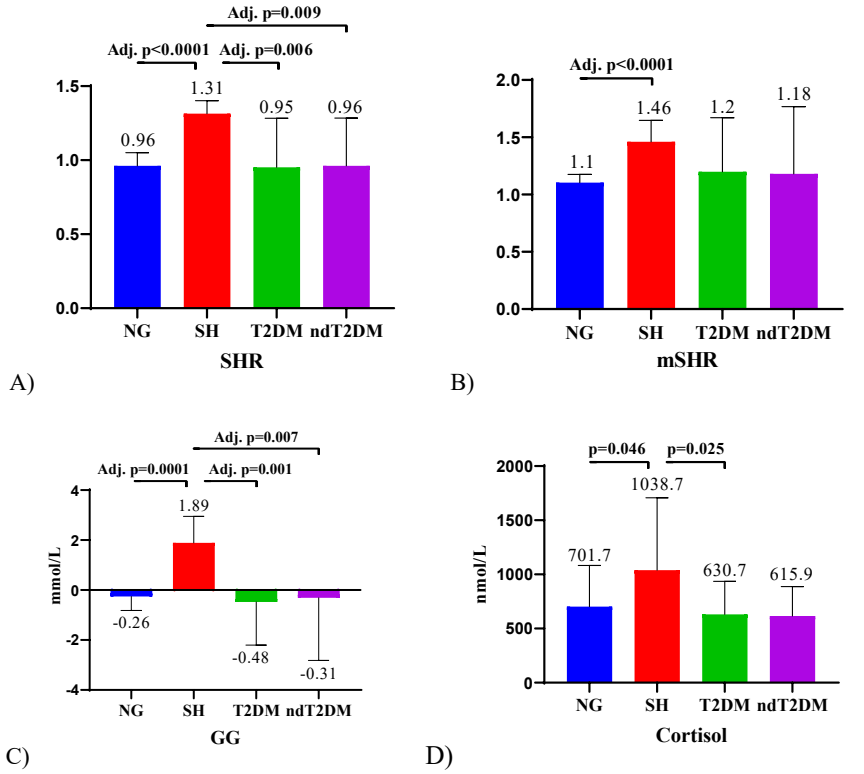


Fig. 20. Comparative analysis of the values of individual HbA1c-based glycemic variables – SHR (A), mSHR (B), GG (C) and cortisol (D) between the groups

2.3.3. Progranulin and TNF-α according to glycemic status

Table 11. Comparative characteristics of PGRN, TNF-α levels and the PGRN/TNF-α ratio

Groups / Parameters	NG (n=26)	SH (n=9)	T2DM (n=14)	ndT2DM (n=6)	F/H, p value
PGRN (ng/mL), median (IQR)	29.04 (23.31–33.86)	36.74 (23.51–43.91)	29.55 (23.35–44.8)	30.77 (21.97–42.69)	H=1.993, p=0.574
TNF-α (pg/mL), mean (SD)	29.68±25.93	42.56±65.43	24.39±13.44	26.23±11.46	F=0.612, p=0.61
PGRN/TNF-α, mean (SD)	1.32±0.69	1.83±1.27	1.77±0.96	1.45±0.77	F=1.217, p=0.313

The markers PGRN and TNF-α, as well as their ratio, also demonstrated the highest levels in the group with SH, although the differences between the groups were not statistically significant (Table 11). Regarding gender distribution, we did not observe significant differences in the respective indicators (PGRN, p=0.39; TNF-α, p=0.313; PGRN/TNF-α, p=0.133).

2.4. Parameters according to AIS severity

We assessed the severity of AIS at admission according to the NIHSS, both in the total cohort and according to the outcome of hospitalization (Fig. 21).

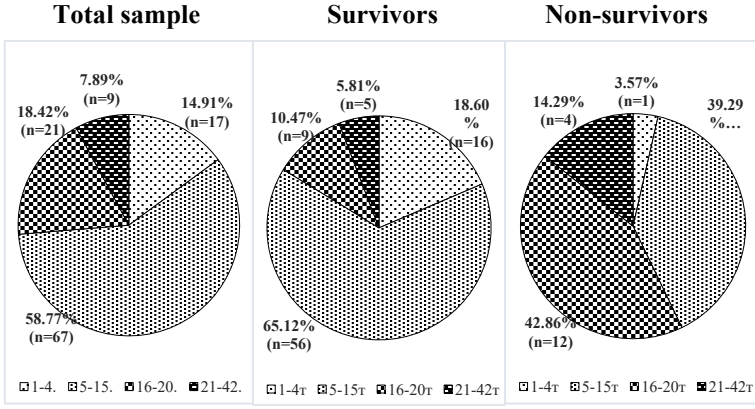


Fig. 21. Distribution of patients by severity of AIS in the total sample and according to the outcome of hospitalization

In the total sample, as well as in the group of surviving patients, we observed a similar distribution of the different degrees of severity of AIS (1-4p., p=0.487; 5-15p., p=0.362; 16-20p., p=0.12; 21-42p., p=0.569) with a predominance of cases with moderate stroke severity (58.77% and 65.12%, respectively). However, in the group of deceased patients, a similar frequency of moderate and moderate to severe AIS was found (39.29% and 42.86% respectively, p= 0.788), with the proportion of moderate AIS being significantly lower than that in the group of surviving patients ($\chi2$=5.765, p=0.016), and the proportion of moderate to severe AIS being significantly higher than that in the general sample ($\chi2$=7.474, p=0.006) and in the group of survivors ($\chi2$=14.614, p=0.0001). Additionally, in patients with a fatal outcome, we observed a higher proportion of severe AIS and the lowest proportion of mild AIS compared to survivors (1-4p., p=0.053; 21-42p., p=0.15) and the total sample (1-4p., p=0.487; 21-42p., p=0.569), although statistical significance was not reached.

2.4.1. Main characteristics of patients according to the severity of AIS (Table 12)

Table 12. Main characteristics of patients according to the severity of AIS

Groups / Parameters	NIHSS 1–4 p. (n=17)	NIHSS 5–15 p. (n=67)	NIHSS 16–20 p. (n=21)	NIHSS 21–42 p. (n=9)	F/H, p value
Gender (males), n (%)	7 (41.18)	32 (47.76)	9 (42.86)	1 (11.11)	F=2.339, p=0.077
Age (years), median (IQR)	74 (63–77)	75 (67-81)	75 (70.5–85)	82 (71.5–85.5)	H=4.798, p=0.187
mRS (p.), median (IQR)	1 (1-1)	3 (1-4)	6 (4–6)	5 (4–6)	**H=42.787, p<0.0001**
NIHSS 2 (p.), median (IQR)	2 (1–2.75)	5 (4–9)	13 (6–15)	16 (13–25)	**H=44.259, p<0.0001**
Hospital stay (days), median (IQR)	4 (4–5)	5 (4–9)	7 (9.5)	10 (2–15)	H=6.202, p=0.102

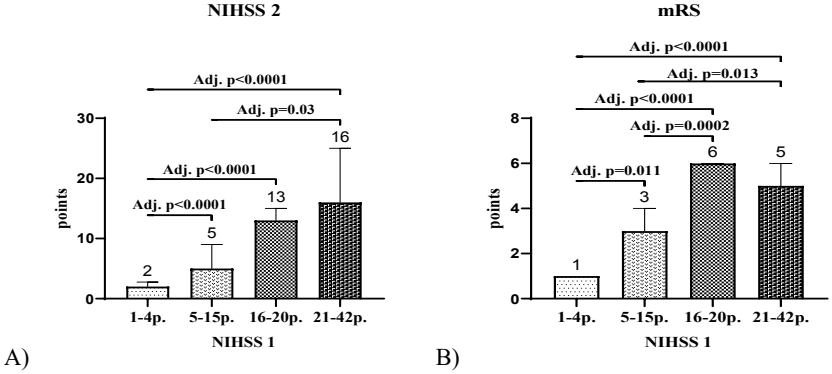


Fig. 22. Comparative analysis of the severity of AIS at discharge (NIHSS 2) (A) and the functional status at discharge (mRS) (B) according to the severity of AIS at admission (NIHSS 1)

We observed an increase in patient age with increasing severity of AIS, as well as a longer hospital stay, although the differences were not significant. There was borderline significance in the gender distribution between the different degrees of stroke severity, with a higher proportion of females, significantly exceeding that of males, especially in the severe AIS group. Statistically significant differences were observed in functional outcome ($p<0.0001$) and severity of AIS at discharge ($p<0.0001$), and there was also a progressive increase with increasing severity of AIS at admission. Subgroup analysis shows that a significant difference in distribution is

not found only between the two highest severity levels of AIS (Fig. 22).

2.4.2. Main laboratory parameters according to the severity of AIS

Among the blood parameters, significant differences were observed in the total leukocyte count (p=0.002) and in particular in the neutrophil count (p=0.003) and eosinophil count (p=0.008). Subgroup analysis revealed significantly higher leukocyte counts in the severe AIS group compared to the lower stroke severity groups (Fig. 23 A), and the neutrophil count in the severe AIS group significantly exceeded that in the mild and moderate AIS groups (Fig. 23 B).

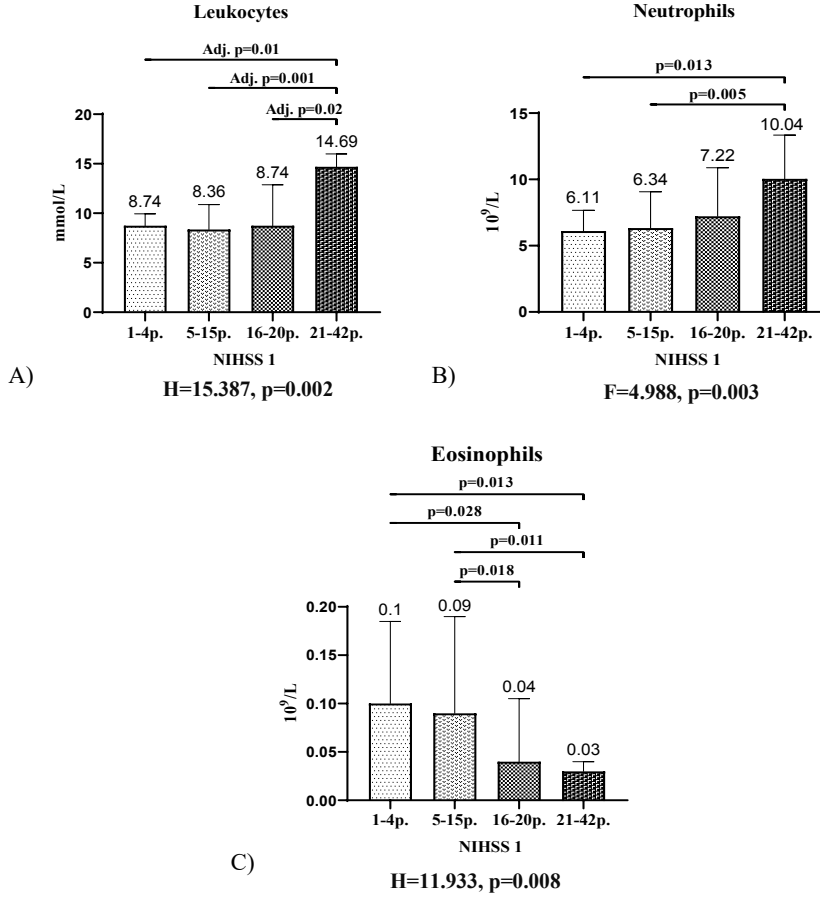


Fig. 23. Comparative analysis of the value of leukocytes (A), neutrophils (B) and eosinophils (C) according to the severity of AIS at admission (NIHSS 1)

Conversely, we observed a decrease in eosinophil counts with increasing stroke severity, with a significant difference between mild and moderate AIS on the one hand and moderate to severe and severe AIS on the other (Fig. 23C). However, these differences did not remain significant after Bonferroni correction.

We also observed that the level of lymphocytes decreased with increasing stroke severity, although no significant difference was found between the groups (p=0.603). However, in the Neutro/Lympho ratio, we reported a borderline significance (p=0.057) between the groups with different severity of AIS, with significantly higher values of the indicator in the group with severe AIS. The remaining biochemical parameters did not demonstrate a significant difference between the groups according to the severity of AIS. Only the CRP levels showed a borderline significance (p=0.058), as we observed a visible increase in its value with increasing stroke severity.

2.4.3. Glycemic and hormonal parameters according to the severity of AIS (Table 13)

Table 13. Comparative characteristics of the studied glycemic and hormonal parameters according to the severity of AIS

Groups / Parameters	NIHSS 1–4 p. (n=17)	NIHSS 5–15 p. (n=67)	NIHSS 16–20 p. (n=21)	NIHSS 21–42 p. (n=9)	F/H, p value
admBG (mmol/L), median (IQR)	6.7 (5.45-8.45)	6.8 (5.8-7.9)	7.5 (6.15-9.0)	8.6 (6.6-15.05)	H=4.765, p=0.19
CV 1-4 (%), median (IQR)	16.57 (9.76-26.16)	13.36 (7.43-24.45)	12.64 (8.18-19.85)	17.04 (7.97-37.08)	H=1.225, p=0.747
CV 2-4 (%), median (IQR)	7.42 (4.76-17.43)	9.6 (6.06-16.74)	9.58 (7.57-17.02)	8.2 (6.46-18.74)	H=0.681, p=0.878
avBG (mmol/L), median (IQR)	5.7 (5.13-6.91)	6.46 (5.63-7.75)	6.65 (5.76-8.76)	7.26 (6.42-8.47)	H=7.135, p=0.068
ΔBG (mmol/L), median (IQR)	2.35 (1.05-4.015)	2 (1.0-3.7)	1.9 (1.0-2.85)	2.4 (1.05-7.62)	H=0.521, p=0.914
HbA1c (%), median (IQR)	6.03 (5.45-6.35)	5.95 (5.6-6.84)	5.94 (5.5-6.26)	6.01 (5.68-6.81)	H=0.328, p=0.955
SHR, mean (SD)	0.98±0.27	1.02±0.34	1.1±0.2	1.42±0.69	**F=3.879, p=0.011**
mSHR, mean (SD)	1.13±0.32	1.2±0.41	1.28±0.23	1.66±0.8	**F=3.702, p=0.014**
GG(mmol/L), mean (SD)	-0.15±1.96	0.31±2.99	0.55±1.57	3.04±4.85	**F=2.757, p=0.046**
Cortisol (nmol/L), median (IQR)	443.9 (323.3-636.1)	594.9 (424.2-772)	777.9 (624.4-1091)	1055 (759.1-1224)	**H=17.603, p=0.001**
Insulin (μIU/mL), median (IQR)	14.95 (8.3-21.63)	10.7 (7.35-20.45)	8.6 (4.6-13.8)	14.1 (5.35-24.2)	H=3.411, p=0.332

We found significant differences between groups with different AIS severity in terms of HbA1c-based glycemic variables (SHR, p=0.011; mSHR, p=0.014; GG, p=0.046), as well as in serum cortisol levels (p=0.001). We observed a progressive increase in these parameters with the severity of stroke. We found the same tendency in admBG, but unlike the parameters for SH, it did not reach statistical significance. Borderline significance was observed with regard to fasting avBG, and again its progressive increase was present with increasing stroke severity.

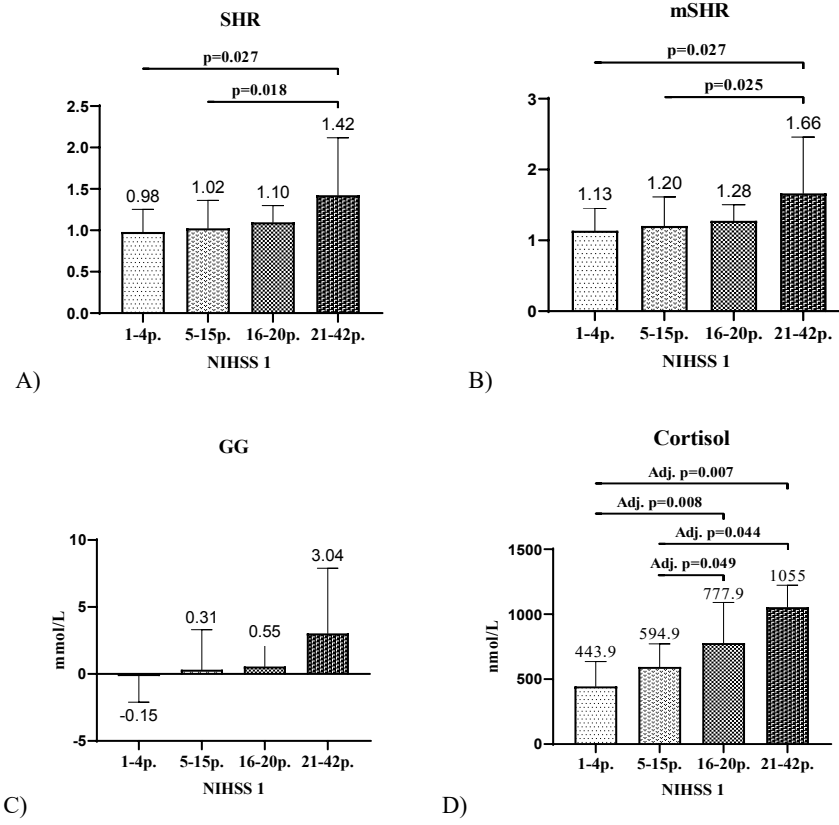


Fig. 24. Comparative analysis of the value of SHR (A), mSHR (B), GG (C) and cortisol (D) between the groups according to the severity of AIS at admission (NIHSS 1)

Subgroup analysis revealed significantly higher values of SHR (Fig. 24 A) as well as mSHR (Fig. 24 B) in patients with severe AIS compared to those with mild and moderate AIS. A similar trend, but with borderline significance, was present with respect to GG (p=0.068 and p=0.072 respectively) (Fig. 24 C). Regarding cortisol levels (Fig. 24 D) – patients with moderate to severe and severe AIS on the one hand, showed significantly higher serum cortisol levels compared to those with mild and moderate AIS on the other.

2.4.4. Progranulin and TNF-α according to the severity of AIS

The comparison of the levels of PGRN, TNF-α and their ratio between patients with different severity of AIS showed a statistically significant difference in all three indicators (PGRN, p=0.012; TNF-α, p=0.024; PGRN/TNF-α, p=0.018), with a visible increase in the value of PGRN with increasing stroke severity and vice versa – highest values of TNF-α in the group with mild AIS and lower values in patients with higher degrees of stroke severity. Subgroup analysis revealed significantly lower PGRN levels (Fig. 25 A) in patients with mild versus moderate and moderate to severe AIS and concomitantly significantly higher TNF-α levels (Fig. 25 B) in the mild versus moderate AIS group. As for the ratio of the two indicators (Fig. 25 C), it demonstrated significantly lower values in the mild versus moderate AIS group.

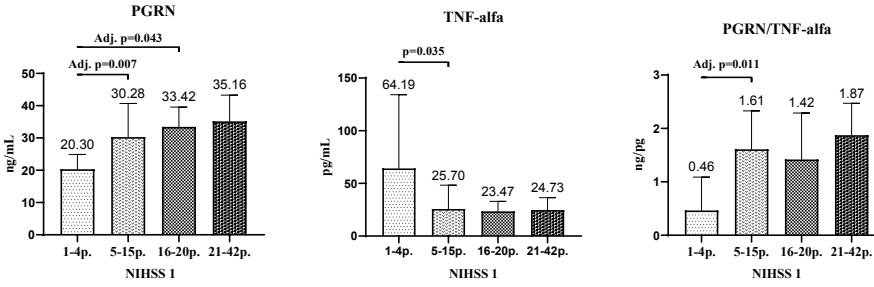


Fig 25. Comparative analysis of the values of PGRN (A), TNF-α (B) and the PGRN/TNF-α ratio (C) according to AIS severity at admission (NIHSS 1)

2.5. Parameters according to AIS outcome

A fatal outcome was observed in 24.56% of patients in the study (n=28). Although not a large proportion of the total sample (n=15/114, 13.16%), the SH group demonstrated a significant proportion of deceased patients (n=8/28, 28.57%) accounting for more than ¼ of all patients with a fatal outcome (Fig. 26).

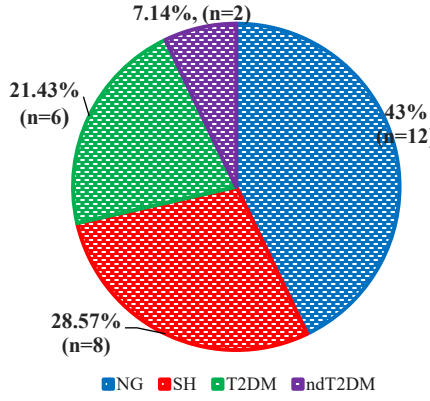


Fig. 26. Distribution of deceased patients according to glycemic status

2.5.1. Main characteristics of patients according to the outcome of AIS (Table 14)

Table 14. Main characteristics of patients according to the outcome of AIS

Groups / Parameters	Survivors (n=86)	Non-survivors (n=28)	χ2/t/U, p value
Gender (males), n (%)	39 (45.35)	15 (53.57)	χ^2=0.567, p=0.451
Age (years), mean (SD)	71.74±11.34	78.18±7.57	**t=2.801, p=0.006**
NIHSS 1 (p.), mean (SD)	9.72±6.31	15.93±5.31	**t=4.69, p<0.0001**
Hospital stay (days), median (IQR)	5 (4-9)	4 (3–8)	**U=815.5, p=0.009**

We did not observe significant differences in terms of gender distribution according to AIS outcome. However, we found that deceased patients were older (p=0.006), were admitted with more severe AIS (p<0.0001) and had a shorter hospital stay (p<0.0001) compared to survivors, and the differences were significant. Regarding RFs for AIS, we reported that patients with a fatal outcome had a significantly higher incidence of atrial fibrillation (χ2=6.439, p=0.011) and HF (χ2=11.011, p=0.001) compared to survivors.

We examined the differences in the parameters between surviving and deceased patients in the groups with different glycemic status and found that although the differences were present in each of the groups, statistical significance was reached only in some of them (age – SH, t=2.935, p=0.012; NIHSS 1 – NG, t=2.606, p=0.011, T2DM, t=3.613, p=0.001, ndT2DM, t=3.637, p=0.007; hospital stay – T2DM, U=21, p=0.01; atrial fibrillation – T2DM, $\chi 2$=6.827, p=0.009; HF – SH, $\chi 2$=4.0, p=0.045). Of interest is the fact that deceased patients presented with significantly more severe AIS in all groups except the one with SH.

2.5.2. Main laboratory parameters according to the outcome of AIS (Table 15)

Table 15. Comparative characteristics of the studied laboratory parameters according to the outcome of AIS

Groups / Parameters	Survivors (n=86)	Non-survivors (n=28)	t/U, p value
ПКК с ДКК			
Hb (g/L), mean (SD)	135.2±20.1	127.9±23.06	t=1.594, p=114
Er (1012/L), mean (SD)	4.62±0.72	4.41±0.78	t=1.266, p=0.208
Hct (L/L), mean (SD)	0.41±0.06	0.39±0.07	t=1.661, p=0.099
Leu (109/l), mean (SD)	9.35±4.0	10.64±3.69	t=1.513, p=0.133
Neutro (109/L), mean (SD)	6.28±2.63	8.23±3.55	**t=3.128, p=0.002**
Eo (109/L), median (IQR)	0.09 (0.03–0.17)	0.06 (0.005–0.13)	U=1005, p=0.19
Baso (109/L), median (IQR)	0.03 (0.02–0.052)	0.02 (0.01–0.047)	**U=858, p=0.021**
Mono (109/L), mean (SD)	0.66±0.26	0.74±0.27	t=1.493, p=0.138
Lympho (109/L), median (IQR)	1.59 (1.14–2.37)	1.08 (0.68–1.68)	**U=749, p=0.002**
Tr (109/L), mean (SD)	248.7±75.7	217.8±91.52	t=1.78, p=0.078
Neutro/Lympho, median (IQR)	3.61 (2.18–5.24)	6.0 (3.27–15.49)	**U=691, p=0.001**
Биохимични показатели			
TC (mmol/L), mean (SD)	5.04±1.27	4.31±1.22	**t=2.689, p=0.008**
HDL-C (mmol/L), median (IQR)	1.16 (0.98–1.53)	1.17 (1.04–1.53)	U=1078, p=0.77
LDL-C (mmol/L), mean (SD)	2.92±1.13	2.41±1.05	**t=2.092, p=0.039**
TG (mmol/L), median (IQR)	1.3 (0.97–2.24)	1.22 (0.91–1.58)	U=960.5, p=0.128
Урея (mmol/L), median (IQR)	6.4 (4.95–9.35)	8.75 (6.1–11.95)	**U=744.5, p=0.003**
Креатинин (μmol/L), median (IQR)	85.5 (68–108.3)	87.5 (70.75–133)	U=1060, p=0.346
eGFR ml/min/1.73m2, median (IQR)	74.5 (51–92.25)	71 (47–84.5)	U=998.5, p=178
ASAT (U/L), median (IQR)	21 (16.85–32.1)	28.15 (17.7–49.75)	U=1007, p=0.196
ALAT (U/L), median (IQR)	17.5 (13.08–24.3)	18.3 (11.28–32.5)	U=1203, p=0.996
CRP (mg/L), median (IQR)	5.88 (2.46–16.28)	10.2 (4.76–57.05)	**U=867.5, p=0.026**

In terms of blood counts, we observed generally higher leukocyte levels in the group of deceased patients, although the difference was not significant. However, differential counting revealed that patients with fatal outcomes showed significantly higher levels of neutrophils (p=0.002) and lower levels of basophils (p=0.021) and lymphocytes (p=0.002) compared to surviving patients. A significantly higher Neutro/Lympho ratio (p=0.001) was also reported in patients with a fatal outcome compared to those with a favorable outcome. Corresponding differences in parameters between surviving and deceased patients were observed in the groups according to glycemic status, but statistical significance was not reached in any of them.

Analysis of lipid parameters revealed significantly lower levels of total cholesterol (p=0.008) and LDL-C (p=0.039) in deceased patients compared to survivors, although no difference in statin treatment was found between the two groups. Similar observations were present between patients with fatal and favorable outcomes in the groups according to glycemic status, which, however, did not show significance. From the rest of the biochemical parameters, we reported significantly higher values in the level of urea (p=0.003) as well as CRP (p=0.026) in the deceased compared to the surviving patients, and in the subgroup analysis these differences were significant only in the NG group (urea, U=152.5, p=0.007; CRP, U=179, p=0.03). Interestingly, with regard to CRP in the other groups, a trend towards lower values was observed in patients with a fatal outcome.

2.5.3. Glycemic and hormonal parameters according to the outcome of the AIS

The comparative analysis of the studied glycemic parameters (Table 16) revealed that although all of them had higher values in the group with deceased patients, the difference was significant only in relation to the fasting avBG during the hospital stay (p=0.023). We found that this relationship was present in all groups, but was significant only for those with NG (t=3.001, p=0.004) and SH (t=3.514, p=0.004).

Additionally, we recorded nearly two times higher cortisol levels in patients with a fatal outcome compared to those who survived AIS, which showed statistical significance (p<0.0001). Subgroup analysis reported significantly higher cortisol levels again in the NG (t=3.509, p=0.001) and SH (t=2.188, p=0.047) groups. We found that the trend for significantly higher cortisol levels in deceased patients was present in both females (survivors, 653.3±295; deceased, 1334±645.8; t=5.482, p<0.0001) and males (survivors, 560.2±267.2; deceased, 822.1±378.2; t=2.863, p=0.006). In addition, we analyzed cortisol

levels among deceased patients by gender and found significantly higher cortisol levels in females (1334±645.8) compared to males (822.1±378.2) with fatal outcome (t=2.605, p=0.015). In surviving patients, we reported no difference in cortisol levels between males and females (males, 560.2±267.2; females, 653.3±295; p=0.134).

Table 16. Comparative characteristics of the studied glycemic and hormonal parameters according to the outcome of AIS

Groups / Parameters	Survivors (n=86)	Non-survivor s (n=28)	t/U, p value
admBG (mmol/L), median (IQR)	6.75 (5.7–8.07)	7.45 (6.61–9.35)	U=966, p=0.118
avBG (mmol/L), mean (SD)	6.83±2.31	7.98±2.11	**t=2.312, p=0.023**
CV 1–4 (%), median (IQR)	14.02 (8.35–23.45)	12.64 (7.9–24.45)	U=1098, p=0.74
CV 2–4 (%), median (IQR)	9.39 (5.98–15.95)	10.51 (7.36–17.52)	U=985, p=0.408
ΔBG (mmol/L), median (IQR)	2.0 (1.0–3.7)	2.0 (1.0–3.6)	U=1134, p=0.929
HbA1c (%), median (IQR)	5.92 (5.57–6.75)	6.18 (5.51–6.42)	U=1110, p=0.595
SHR, median (IQR)	0.99 (0.85–1.17)	1.12 (0.92–1.3)	U=949, p=0.11
mSHR, median (IQR)	1.14 (0.99–1.33)	1.31 (1.09–1.5)	U=931.5, p=0.086
GG (mmol/L), median (IQR)	(–0.07)((–1.06)–1.06)	0.89 ((–0.58)–2.14)	U=974, p=0.152
Cortisol (nmol/L), mean (SD)	610.5±284.8	1060±572.1	**t=5.494, p<0.0001**
Insulin (μIU/mL), median (IQR)	11.1 (7.9–19.9)	11.25 (4.42–17.63)	U=869, p=0.414

2.5.4. Progranulin and TNF-α according to the outcome of AIS

The analysis of PGRN, TNF-α and their ratio did not report significant differences between the groups with a favorable and fatal outcome (PGRN, p=0.812; TNF-α, p=0.661; PGRN/TNF-α, p=0.811).

2.6. Correlational analysis of parameters of severity and outcome of AIS (Table 17)

Table 17. Correlation analysis of the parameters of severity and outcome of AIS with some of the other parameters

	NIHSS 1	NIHSS 2	mRS	Fatal outcome	Hospital stay
Age	**r_s=0.239 p=0.01**	r_s=0.142 p=0.21	**r_s=0.261 p=0.005**	**r_s=0.249 p=0.008**	r_s=(–0.164) p=0.082
Number of RFs	**r_s=0.226 p=0.016**	r_s=0.135 p=0.236	**r_s=0.192 p=0.041**	r_s=0.158 p=0.092	r_s=(–0.009) p=0.922
NIHSS1	---	**r_s=0.916 p<0.0001**	**r_s=0.761 p<0.0001**	**r_s=0.441 <0.0001**	r_s=0.177 p=0.059
Leu	**r=0.372 p<0.0001**	r_s=0.154 p=0.174	**r_s=0.208 p=0.026**	r_s=0.178 p=0.058	**r_s=0.226 p=0.016**
Neutro	**r=0.371 p<0.0001**	r_s=0.126 p=0.267	**r_s=0.29 p=0.002**	**r_s=0.267 p=0.004**	r_s=0.172 p=0.067
Neutro/ Lympho	**r_s=0.218 p=0.02**	r_s=0.09 p=0.428	**r_s=0.354 p=0.0001**	**r_s=0.318 p=0.001**	r_s=0.05 p=0.595
CRP	**r_s=0.272 p=0.004**	r_s=0.18 p=0.117	**r_s=0.288 p=0.002**	**r_s=0.208 p=0.026**	**r_s=0.218 p=0.021**
Cortisol	**r=0.391 p<0.0001**	**r_s=0.262 p=0.02**	**r_s=0.392 p<0.0001**	**r_s=0.39 p<0.0001**	r_s=0.02 p=0.833
PGRN	**r_s=0.275 p=0.042**	**r_s=0.351 p=0.036**	r_s=0.088 p=0.523	r_s=0.0 p=1	r_s=0.117 p=0.396
avBG	r=0.13 p=0.31	r_s=0.207 p=0.067	**r_s=0.357 p=0.0001**	**r_s=0.329 p=0.0004**	r_s=0.026 p=0.786
SHR	**r_s=0.222 p=0.018**	r_s=0.06 p=0.601	r_s=0.183 p=0.052	r_s=0.151 p=0.109	r_s=0.097 p=0.306
mSHR	**r_s=0.232 p=0.014**	r_s=0.062 p=0.593	r_s=0.198 p=0.036	r_s=0.162 p=0.086	r_s=0.116 p=0.223
GG	**r_s=0.197 p=0.037**	r_s=0.045 p=0.696	r_s=0.156 p=0.099	r_s=0.136 p=0.152	r_s=0.075 p=0.43

Correlation analysis showed that the severity of AIS at admission was weakly positively associated with the age of patients and with the number of RFs for AIS, moderately strongly with lethal outcome, and very strongly with the severity of stroke at discharge and with functional outcome. Even after

adjustment for age and RFs for AIS, we found that the association of AIS severity at admission with the severity at discharge (r_s=0.85, p<0.0001), with the functional outcome (r_s=0.663, p<0.0001) and with the lethal outcome (r_s=0.336, p=0.001) remained. In addition, patients' age showed a weak positive association with functional outcome and fatal outcome that appeared to be independent of their gender (mRS, r_s=0.264, p=0.005; fatal outcome, r_s=0.281, p=0.003), and the number of RFs was also weakly correlated with functional outcome.

No correlation was found between the severity and outcome indicators of AIS with the red blood cell parameters or platelets, but there was a correlation with the total leukocyte count, which was moderately positively associated with the severity of AIS at admission and weakly with the functional outcome and hospital stay.

Neutrophil count also showed a direct moderate association with the severity of AIS at admission and a weak association with functional and fatal outcome, which persisted even after adjustment for age and RFs for AIS (NIHSS 1, r=0.353, p<0.0001; mSR, r_s=0.351, p=0.0001; fatal outcome, r_s=0.290, p=0.003). On the other hand, a weak negative relationship was found between the severity of AIS at admission and the number of eosinophils (r_s=(-0.256), p=0.006), between the functional outcome on the one hand and the number of eosinophils (r_s=(-0.24), p=0.01), basophils (r_s=(-0.271), p=0.003) and lymphocytes (r_s=(-0.293), p=0.002) on the other, as well as between the lethal outcome and the number of basophils (r_s=(-0.217), p=0.02) and lymphocytes (r_s=(-0.282), p=0.002 The Neutro/Lympho ratio ultimately also demonstrated a weak positive association with the severity of AIS at admission, as well as a moderate one with functional outcome and fatal outcome. After adjusting for age and RFs for AIS, the observed relationships persisted (NIHSS 1, r_s=0.256, p=0.009; mSR, r_s=0.318, p=0.01; fatal outcome, r_s=0.369, p=0.0001). In contrast to neutrophils, in which after adjustment for the severity of AIS the association with fatal outcome (p=0.097) and functional outcome (p=0.222) was lost, that of Neutro/Lympho ratio was preserved (mRS, r_s=0.237, p=0.012; fatal outcome, r_s=0.319, p=0.001).

Among lipid parameters, a weak negative relationship was found between total cholesterol and functional outcome (r_s=(-0.188), p=0.045) and with fatal outcome (r_s=(-0.229), p=0.014). We reported that after adjusting for statin treatment, these associations persisted (mRS, r_s=(-0.229), p=0.015; fatal outcome, r_s=(-0.251), p=0.007), as well as after adjustment for cortisol level (mRS, r_s=(-0.216), p=0.022; fatal outcome, r_s=(-0.225), p=0.017). In particular, LDL-C levels showed a similar association with fatal outcome (r_s=(-0.193), p=0.043), again unaffected by statin treatment (r_s=(-0.199), p=0.038), but not by cortisol levels (p=0.055).

Both the severity of AIS at admission and the functional outcome of stroke positively correlated with the urea level (r_s=0.223, p=0.017 and r_s=0.317, p=0.001, respectively) and negatively with the value of the estimated glomerular filtration (r=(-0.225), p=0.016 and r_s=(-0.186), p=0.047, respectively). A weak positive association was also found between fatal outcome and urea level (r_s=0.28, p=0.003). After adjustment for the severity of AIS at admission, we found that the association of urea with functional outcome (r_s=0.256, p=0.006) and fatal outcome (r_s=0.238, p=0.012) was maintained, while that of eGFR with functional outcome was lost (p=0.487).

The CRP value showed a positive weak association with all clinical indicators except the severity of AIS at discharge. After adjustment for age and RFs for AIS, we found that the association of CRP with admission severity (r_s=0.265, p=0.007), with functional outcome (r_s = 0.299, p = 0.002) and with lethal outcome (r_s=0.302, p=0.002) was maintained, unlike that with length of hospital stay (p=0.624). Additionally, after adjusting for the severity of AMI on admission, we reported that the association of CRP with mortality remained (r_s=0.224, p=0.017), but not with functional outcome (p=0.07) or length of hospital stay (p=0.484).

Cortisol levels showed a positive, mostly moderate relationship with all clinical indicators except length of hospital stay. The associations persisted even after adjustment for age and RFs for AIS (NIHSS1, r=0.359, p<0.0001; NIHSS2, r_s=0.279, p=0.022; mRS, r_s=0.368, p<0.0001; fatal outcome, r_s=0.383, p<0.0001), and in particular with the presence of diabetes (NIHSS1, r=0.386, p<0.0001; mRS, r_s=0.433, p<0.0001; fatal outcome, r_s=0.461, p<0.0001) excluding severity of AIS at discharge (p=0.081). After adjusting for renal function, the positive associations of cortisol with the severity of AIS at admission (r=0.351, p<0.0001), with functional outcome (r_s=0.403, p<0.0001) and with mortality (r_s=0.447, p<0.0001) were maintained, but not with the severity of AIS at discharge (p=0.09). The results after adjustment for gender were also similar (NIHSS1, r=0.367, p<0.0001; NIHSS2, p=0.085; mRS, r_s=0.433, p<0.0001; fatal outcome, r_s=0.487, p<0.0001). We also tested whether the association of cortisol with outcome measures would persist after adjustment for the severity of AIS at admission and found an association with functional outcome (r_s=0.243, p=0.01) and mortality (r_s=0.362, p=0.0001), but not with the severity of AIS at discharge (p=0.187). We obtained similar results regarding the association of cortisol with outcome measures and after adjustment for lipid parameters and statin treatment (mRS, r_s=0.416, p=0.0001; NIHSS2, p=0.085; fatal outcome, r_s=0.457, p=0.0001).

The PGRN value was weakly positively correlated with the severity of AIS at admission and moderately strongly with that at discharge. Both relationships persisted after adjusting for patient age (NIHSS1, r=0.317, p=0.019; NIHSS2,

r_s=0.423, p=0.011), but not after adjusting for renal function, where only the association with the severity of AIS at discharge remained (NIHSS1, p=0.08; NIHSS2, r_s=0.368, p=0.03). In addition, when considering the presence of DM, there was only a borderline significant association with the severity of AIS at discharge (NIHSS1, p=0.19; NIHSS2, r_s=0.326, p=0.056).

Among the glycemic indicators, fasting avBG level moderately positively correlated with functional outcome from AIS, as well as with fatal outcome. For both indicators, the association with fasting savBG was preserved even after adjustment for age and RFs for AIS (mRS, r_s=0.325, p=0.001; fatal outcome, r_s=0.326, p=0.001), as well as after taking into account the presence of diabetes (mRS, r_s=0.371, p=0.0001; fatal outcome, r_s=0.333, p=0.0004). The relationship of fasting avBG with the severity of AIS at discharge also showed borderline significance.

In contrast to admBG, HbA1c-based glycemic variables demonstrated a positive weak association with the severity of AIS at admission, which persisted even after adjustment for age and RFs for AIS (SHR, r_s=0.358, p=0.0001; mSHR, r_s=0.34, p=0.001; GG, r_s=0.281, p=0.004) and after adjusting for the presence of diabetes alone (SHR, r_s=0.333, p=0.0001; mSHR, r_s=0.32, p=0.001; GG, r_s=0.27, p=0.004). Additionally, mSHR showed a weak direct correlation with functional outcome, which, however, was lost after adjustment for severity of AIS at admission (p=0.191), age and RFs for AIS (p=0.198), and also after taking into account the presence of diabetes alone (p=0.12). In connection with this observation, we investigated in more detail the association of glycemic variables with this indicator separately in patients without diabetes (NG and SH) and in those with diabetes (T2DM and ndT2DM). Interestingly, we found that in this subgroup analysis all HbA1c-based glycemic variables demonstrated a positive association with functional outcome in patients without diabetes (SHR, r_s=0.301, p=0.008; mSHR, r_s=0.349, p=0.002; GG, r_s=0.301, p=0.008), but in those with diabetes such a relationship did not exist (SHR, p=0.945; mSHR, p=0.893; GG, p=0.957).

For the indicators of GV, as well as HbA1c and admBG, we did not report significant relationships with the indicators of severity and outcome of AIS. Only the relationship of CV 1-4 with the severity of AIS at discharge (p=0.062) and that of ΔBG with the duration of hospital stay showed borderline significance (p=0.064).

2.7. Linear regression analysis for predicting severity of AIS

In order to establish the linear combination between the severity of AIS at admission and its positively correlated indicators (*age, number of RFs, leukocytes, neutrophils, Neutro/Lympho ratio, urea, CRP, SHR, mSHR, GG, cortisol* and *PGRN*) a multiple linear regression analysis was performed. The model composed of all twelve independent variables was statistically significant, F=2.649, p=0.01, and the value of the adjusted coefficient of determination (adjusted R^2) was R^2=0.268. This indicates that 26.8% of the variation in AIS severity could be explained by this regression model. Since the regression coefficients (B) of not all independent variables were statistically significant, a linear regression was performed using the inverse method, successively excluding variables that did not have sufficient influence on the dependent variable. The final reduced regression model included six independent variables – *age, leukocytes, urea, SHR, GG* and *PGRN* and was statistically significant: F=5.212, p<0.001. The value of the adjusted coefficient of determination was R^2=0.319, indicating that 31.9% of the variation in the severity of AIS could be explained by this regression model. The regression coefficient of SHR was the largest (B=17.575, p=0.01), from which we can conclude that it contributes to the prediction of the severity of AIS to the greatest extent. It was followed by leukocytes (B=0.529, p=0.009) and PGRN (B=0.261, p=0.004), and the value of the regression constant was (-32.622).

2.8. Logistic regression analysis for predicting mortality outcome

Logistic regression was constructed to assess whether the independent variables *age, NIHSS 1, neutrophils, Neutro/Lympho ratio, urea, CRP, avBG* and *cortisol*, with which a positive correlation was found, statistically significantly predicted the death outcome. When all eight independent variables were considered simultaneously, they statistically significantly predicted mortality: $\chi 2$=41.746, df=8, p<0.001. Since not all independent variables were statistically significant according to the Wald criterion, a logistic regression was performed using the inverse method, successively excluding variables that did not have sufficient influence on the dependent variable. The final reduced regression model included four independent variables – *NIHSS 1, Neutro/Lympho ratio, avBG* and *cortisol* and was statistically significant: $\chi 2$=37.578, df=4, p<0.001. The model explained between 28.7% (Cox & Snell R^2) and 42.8% (Nagelkerke R^2) of the variance in AIS outcome and correctly classified 85.6% of the observations (94% of surviving patients and 59.3% of those with fatal outcome). The Wald criterion showed that three of the independent variables *NIHSS 1*

(p=0.033), *avBG* (p=0.045) and *cortisol* (p=0.007) significantly influenced the prognosis of the outcome of AIS, with the values of their regression coefficients (B) being 0.096, 0.216 and 0.002, respectively, and the value of the regression constant was (-6.145). The exponent of the regression coefficient Exp (B) showed that an increase in NIHSS 1 by 1 SD leads to an increase in the chance of death by 1.1 folds, an increase in avBG by 1 SD increases the chance of death by 1.241 folds, and that of cortisol by 1 SD – by 1.002 folds.

2.9. Correlation analysis of glycemic parameters (Table 18)

Table 18. Correlation analysis of glycemic parameters with some of the other parameters

	admBG	SHR	mSHR	GG
Leu	**r_s=0.262 p=0.005**	**r_s=0.245 p=0.009**	**r_s=0.246 p=0.008**	**r_s=0.238 p=0.011**
Neutro	**r_s=0.381 p<0.0001**	**r_s=0.407 p<0.0001**	**r_s=0.413 p<0.0001**	**r_s=0.392 p<0.0001**
Eo	**r_s=(–0.289) p=0.002**	**r_s=(–0.383) p<0.0001**	**r_s=(–0.379) p<0.0001**	**r_s=(–0.345) p=0.0002**
Baso	r_s=(–0.151) p=0.109	**r_s=(–0.245) p=0.009**	**r_s=(–0.242) p=0.01**	**r_s=(–0.231) p=0.014**
Lympho	**r_s=(–0.24) p=0.01**	**r_s=(–0.332) p=0.0003**	**r_s=(–0.331) p=0.0003**	**r_s=(–0.311) p=0.001**
Neutro/ Lympho	**r_s=0.383 p<0.0001**	**r_s=0.456 p<0.0001**	**r_s=0.463 p<0.0001**	**r_s=0.433 p<0.0001**
CRP	**r_s=0.366 p<0.0001**	**r_s=0.355 p=0.0001**	**r_s=0.378 p<0.0001**	**r_s=0.339 p=0.0003**
Cortisol	**r_s=0.218 p=0.02**	**r_s=0.301 p=0.001**	**r_s=0.272 p=0.004**	**r_s=0.288 p=0.002**
Insulin	**r_s=0.241 p=0.015**	r_s=0.047 p=0.641	r_s=0.1 p=0.322	r_s=0.062 p=0.541

In addition to the already found dependencies with the parameters of severity and outcome of AIS, we found that admBG was positively associated with some inflammatory indicators such as leukocyte count, neutrophil count, as well as CRP. Also positive was the association with plasma cortisol and insulin levels. Negatively associated with admBG were the values of eosinophils and lymphocytes. Finally, we also observed a positive relationship with the Neutro/Lymph ratio.

Similar correlations were found with all three HbA1c-based glycemic variables. We observed a weak positive correlation with leukocyte count and a moderately strong one with neutrophil count, as well as with the Neutro/Lymph ratio. Of the remaining indicators of the differential blood count, a negative association was found with the number of eosinophils, basophils and lymphocytes. Additionally, a moderately strong positive association was found with the level of CRP, and also a weak one with plasma cortisol. We did not observe an association with the level of PGRN, TNF-α or their ratio.

Fasting srCG during the course of the stay also showed a positive association with the level of CRP (r_s=0.279, p=0.003), as well as with the Neutro/Lympho ratio (r_s=0.19, p=0.043). It also showed a relationship with lipid parameters, in particular a negative one with the level of HDL-C (r_s=(-0.304), p=0.001) and a positive one with TG (r_s=0.225, p=0.017).

Glycated hemoglobin was the only one that showed a correlation with the number of RFs for AIS (r_s=0.198, p=0.035). Like fasting avBG, it was also negatively associated with HDL-C levels (r_s=(-0.278), p=0.003) and positively with TG (r_s=0.286, p=0.002).

The variability of BG, expressed by the parameters including the highest levels of BG, namely CV 1-4 and ΔBG, showed a positive relationship with the platelet count as well as with the PGRN/TNF-α ratio. When excluding the first day of hospitalization, CV 2-4 was negatively associated with patients' age (r=(-0.237), p=0.012), but also with the TNF-α level (r_s=(-0.321), p=0.017). We observed a positive association with the number of eosinophils (r_s=0.208, p=0.029) and basophils (r_s=0.21, p=0.027), as well as with the PGRN/TNF-α ratio (r_s=0.35, p=0.009).

2.10. Correlation analysis of cortisol, insulin, PGRN, TNF-α and the PGRN/TNF-α ratio

Plasma cortisol level revealed the most dependencies. It showed a positive association with the age of the patients (r_s=0.242, p=0.01) and the number of RFs for AIS (r_s=0.224, p=0.017). Additionally, it was positively associated with moderate strength with inflammatory indicators such as leukocyte count

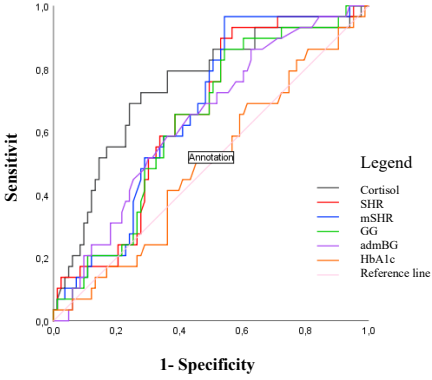
(r=0.383, p<0.0001), neutrophils (r=0.371, p<0.0001), CRP (r_s=0.349, p=0.0002), and also weakly with the Neutro/Lympho ratio (r_s=0.256, p=0.006), TNF-α (r=0.268, p=0.043), urea level (r_s=0.236, p=0.012) and ASAT (r_s=0.222, p=0.018). There was a weak negative correlation between cortisol and red blood cell count (r=(-0.278), p=0.003), hematocrit level (r=(-0.191), p=0.042), eosinophils (r_s=(-0.277), p=0.003), platelets (r=(-0.191), p=0.042), and estimated glomerular filtration rate (r=(-0.278), p=0.003). We did not find a correlation between cortisol level and lipid parameters or statin treatment.

Insulin, in turn, showed a negative weak association with the age of the patients (r_s=(-0.209), p=0.036). It demonstrated a positive relationship with the number of RFs for AIS (r_s=0.211, p=0.034), with the number of basophils (r_s=0.306, p=0.002) and lymphocytes (r_s=0.238, p=0.016), as well as with all lipid parameters except HDL-C (TC, r_s=0.22, p=0.027; LDL-C, r_s=0.274, p=0.007; TG, r_s=0.232, p=0.02), showing a borderline correlation dependence on statin treatment. In this regard, we investigated whether the association between insulin and lipid parameters was maintained after adjustment for statin treatment and reported that it persisted for TG (r_s=0.253, p=0.012), but not for total cholesterol (p=0.264) or LDL-C (p=0.237).

The marker PGRN demonstrated a moderate direct correlation with red blood cell parameters (Hb, r_s=0.442, p=0.001; Er, r_s=0.403, p=0.002; Hct, r_s=0.487, p=0.0002), as well as with platelets (r_s=0.475, p=0.0002) and a strong one with total cholesterol (r_s=0.517, p<0.0001) and LDL-C (r_s=0.599, p<0.0001). After correction with statin treatment, the dependencies with total cholesterol (r_s=0.45, p=0.001) and LDL-C (r_s=0.548, p=0.0001) are preserved. Additionally, a negative association was found between PGRN on the one hand and urea level (r_s=(-0.332), p=0.013) and TNF-α (r_s=(-0.297), p=0.028) on the other. At the same time, TNF-α was weakly negatively associated with hemoglobin (r=(-0.267), p=0.044), hematocrit (r=(-0.287), p=0.03), platelets (r=(-0.295), p=0.026) and HDL-C (r_s=(-0.273), p=0.045), and also moderately positively with creatinine level (r_s=0.343, p=0.009) and CRP (r_s=0.358, p=0.006). However, the association with HDL-C was lost after adjustment for statin treatment (p=0.169). HDL-C was lost after adjustment for statin treatment (p=0.169). Ultimately, the relationship between these two parameters was in a moderate positive relationship with hemoglobin (r_s=0.315, p=0.019), erythrocytes (r_s=0.312, p=0.02), hematocrit (r_s=0.371, p=0.005), platelets (r_s=0.305, p=0.024), total cholesterol (r_s=0.368, p=0.006) and LDL-C (r_s=0.364, p=0.008), as well as in a moderate negative relationship with urea (r_s=(-0.372), p=0.005) and creatinine (r_s=(-0.383), p=0.004). After adjusting for ongoing statin treatment, the associations with total cholesterol (r_s=0.309, p=0.023) and LDL-C (r_s=0.314, p=0.025) were maintained.

2.11. ROC analysis of cortisol, HbA1c-based glycemic variables, admBG and chronic glycemic control for the development of moderate to severe and severe AIS

We performed a ROC analysis in which we examined measures of stress response such as cortisol and HbA1c-based glycemic variables, as well as admBG and chronic glycemic control (HbA1c), to determine which of these could predict the development of moderate to severe and severe AIS (NIHSS1 >15) (Fig. 27).



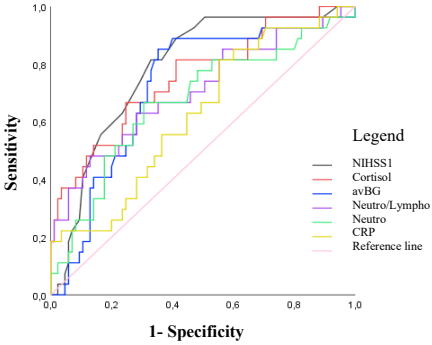
	AUC	95%CI	p value
Cortisol	0.74	0.634-0.846	**0.0001**
SHR	0.652	0.546-0.758	**0.015**
mSHR	0.665	0.561-0.768	**0.008**
GG	0.636	0.526-0.745	**0.03**
admBG	0.619	0.504–0.733	0.054
HbA1c	0.502	0.382–0.623	0.97

Fig. 27. ROC curve of cortisol, HbA1c-based glycemic variables, admBG and HbA1c for the development of moderate to severe and severe AIS (NIHSS1 >15)

The largest area under the curve (AUC) was reported for cortisol, followed by HbA1c-based glycemic variables, and for all the results were statistically significant. Lower and borderline significant was the area under the curve for prCG and insignificant for HbA1c. We determined the optimal cortisol threshold value above which the risk of developing moderate to severe and severe AIS increases to 741.4 nmol/L (Se 73.33%, Sp 72.29%). For SHR, the optimal threshold value is 0.933 (Se 89.66%, Sp 46.43%), for mSHR – 1.065 (Se 96.55%, Sp 45.24%), and for GG – (-0.504) mmol/L (Se 86.21%, Sp 45.24%).

2.12. ROC analysis of AIS severity, cortisol, avBG, Neutro/Lympho ratio, neutrophils, and CRP for death outcome

We performed ROC analysis examining parameters correlated with mortality to determine which had the greatest prognostic value (Fig. 28). The largest area under the curve was reported for the severity of AIS at admission, followed by cortisol, avBG, Neutro/Lympho ratio, neutrophil count, and lastly CRP, all of which were statistically significant.



	AUC	95%CI	p value
NIHSS 1	0.795	0.705-0.885	**<0.0001**
Cortisol	0.76	0.654-0.867	**<0.0001**
avBG	0.723	0.615-0.83	**0.001**
Neutro/ Lympho	0.713	0.595-0.831	**0.001**
Neutro	0.679	0.559-0.8	**0.004**
CRP	0.64	0.523-0.756	**0.027**

Fig. 28. ROC curve of severity of AIS at admission, cortisol, avBG, Neutro/Lympho ratio, neutrophils and CRP for fatal outcome

As the optimal threshold value of NIHSS1, above which the risk of death increases, we determined 9.5 points (Se 89.29%, Sp 59.3%). Regarding cortisol, the optimal threshold value is 762.2 nmol/L (Se 67.86%, Sp 75.29%), for avBG – 6.525 mmol/L (Se 85.19%, Sp 65.12%), for the Neutro/Lympho ratio – 6.403 (Se 50.0%, Sp 86.05%), for the neutrophil count – 6.765 109/L (Se 67.86%, Sp 68.6%), and for CRP – 4.53 mg/L (Se 82.14%, Sp 44.19%).

V. DISCUSION

1. Prevalence of stress hyperglycemia in patients with acute ischemic stroke

In our study, we found similar distribution of SH in AIS, which is in accordance to the published data, namely 20.9% and 13.16% in stage I and stage II of the study, respectively. The observed differences inevitably lie in the way patients are divided into groups and, in particular, in the use of HbA1c to distinguish them.

We observed a significant proportion of patients with ndT2DM in the II stage of the study, namely 8.77%. The lack of HbA1c testing in their case would lead to misinterpretation of the results and consequently missed or delayed diagnosis, as well as treatment of this chronic disease. We also found a significant proportion of patients with prediabetes, as many as 39.47% of the total sample. All of them have the potential to develop diabetes in the future in the absence of preventive measures.

In summary, in more than ¾ of the patients included in the II stage of the study, we found abnormal glycemic status, which eloquently shows how widespread glycemic disorders are in patients during the course of AIS. This necessitates the need to clarify the glycemic status of these patients, beyond routine monitoring of BG during the hospital stay.

2. HbA1c-based glycemic variables versus admission blood glucose for assessment of stress hyperglycemia

We observed a significantly greater severity of AIS in the group with SH compared to those with NG and ndT2DM, and the proportion of patients with moderate to severe and severe AIS was significantly greater in the group with SH compared to the other three groups. In contrast to admBG, the HbA1c-based glycemic variables, taking into account the background glycemia, demonstrated the highest values precisely in the group with SH, significantly higher compared to the other three groups. Serum cortisol, similar to glycemic variables and severity of AIS at admission, showed significantly higher values in the group with SH compared to the control group with NG and that with T2DM. Additionally, we observed a significant difference in cortisol levels and HbA1c-based glycemic variables between different degrees of AIS severity, as well as a tendency for their progressive increase with the severity of stroke. We found the same tendency in relation to admBG, however, without registering statistical

significance.

Both cortisol and glycemic variables, but not admBG, positively and independently, in particular of diabetic status, correlated with the severity of AIS at admission. The positive association of cortisol with the severity of AIS confirms that its levels reflect the severity of stress response. The corresponding values of the HbA1c-based glycemic variables lead us to conclude that, taking into account the influence of background glycemia, they are better determinants of stress response than admBG.

This statement is also supported by the results obtained from the ROC analysis, which demonstrates the significance of serum cortisol, followed by glycemic variables, but not admBG, in predicting the development of moderate to severe and severe AIS. Regression analysis of parameters correlated with stroke severity reported the largest regression coefficient for SHR, indicating that it contributes the most to predicting AIS severity.

In summary, we reported that SH is associated with more severe AIS, and that HbA1c-based glycemic variables provide a better assessment of stress response compared to absolute BG, regardless of the presence of DM. In addition, we found that serum cortisol levels could be used to adequately assess the severity of AIS.

3. Factors associated with the severity of acute ischemic stroke

In stage I of our study, we observed a positive correlation of nonfatal stroke severity with patients' age and white blood cell count and a negative correlation with HDL-C level. We observed a significant difference in the level of admBG between the groups with different severity of nonfatal AIS, but a significant increase was only present up to the level of moderate non-fatal stroke. This could explain the lack of association between admBG level and severity of non-fatal AIS at admission, but we still cannot rule out the possibility of one in fatal AIS.

In stage II of our study, as we have already noted, admBG again showed no correlation with the severity of AIS at admission, although we observed its progressive increase with stroke severity. However, an association was present for HbA1c-based glycemic variables, more accurately reflecting stress hyperglycemia. Of the remaining glycemic parameters, we only reported a borderline significant difference in fasting avBG between the groups with different severity of AIS, again with a progressive increase in values with stroke severity, but no established relationship in the correlation analysis. Glycated hemoglobin, as well as indicators of glycemic variability, also did not

demonstrate an association with the severity of AIS. Of interest are the results of the ROC analysis for the development of moderate to severe and severe stroke, in which glycemic variables demonstrated significance, but not admBG or chronic glycemic control in the face of HbA1c.

In stage II, we also confirmed the positive correlation of the severity of AIS with the age of the patients, as well as with the leukocyte count. The analysis of DBC further revealed a positive association with the neutrophil count and a negative one with the eosinophil count. As already noted, the severity of AIS also positively correlated with serum cortisol, which in turn showed the same associations with the leukocyte, neutrophil and eosinophil counts.

There is a lot of evidence in the literature regarding the white blood cell count and its relationship with the severity and especially the prognosis of AIS. The anti-inflammatory effects of glucocorticoids are well known as their ability to suppress the immunological response occurs at different levels – reduction in the number of lymphocytes in the peripheral blood, increase in the number of neutrophils, decrease in eosinophils, inhibition of monocyte proliferation and differentiation. Given these effects of glucocorticoids, it is logical to observe changes in the white blood cell count during various stressful conditions, in which cortisol levels are elevated. They are the basis of the so-called "stress leukogram" consisting of lymphopenia, eosinopenia, neutrophilia, and monocytosis. Similar changes, but with a predominant neutrophilia of immature neutrophils, occur in inflammatory conditions and infections. In this way, we can also explain the association of white blood cells with the severity of AIS, considering that as the severity of the stroke increases, there is a more pronounced stress reaction, correspondingly higher cortisol levels, as well as frequent concomitant infections, further worsening the condition.

The observed changes in leukocytes under stress conditions are a widely available and easy-to-use indicator, leading to the expansion of their use and the study of ratios between individual leukocyte subpopulations in order to search for a more accurate prognostic marker. The Neutro/Lympho ratio, widely studied in recent years, demonstrates a borderline significant difference between groups with different AIS severity, with the highest levels in patients with severe stroke, and correlation analysis confirmed the results of other researchers for a positive association of the indicator with the severity of AIS at admission.

The inflammatory marker CRP also demonstrates a positive correlation with the severity of AIS, which is also supported by other teams (Liu C, 2022; Lasek-Bal A, 2019).

As expected, it was found that as the number of risk factors increases, so does the severity of AIS, which emphasizes the polymorbidity of these patients and the need for adequate control of each factor separately. Given that

comorbidities increase with age, the existing relationship between patient age and stroke severity is also explained.

We found a positive correlation between the severity of AIS and urea levels, and although no relationship was observed with creatinine levels, a negative one was present with renal function represented by the estimated glomerular filtration rate. Despite these observations, we found that renal function did not influence the association of AIS severity at admission with serum cortisol, considering its urinary excretion.

We observed a significant difference between groups with different severity of AIS in the levels of PGRN, TNF-α and their ratio. The two indicators showed an inverse relationship with each other and, accordingly, demonstrated an opposite change with increasing stroke severity, namely an increase in PGRN levels and a decrease in TNF-α levels, and ultimately a significant increase in their ratio. Considering the complex relationship between the two indicators, their ratio seems crucial to determine the inflammatory microenvironment in patients. However, a correlation with the severity of AIS was found only with respect to the level of PGRN and it was positive. And although this relationship was shown to be dependent on other variables, it deserves our attention given that the regression analysis of the indicators correlating with the severity of AIS in addition, after SHR, determined the highest regression coefficients for the leukocyte count and the PGRN level, taking into account their role in predicting the severity of AIS.

We could summarize that the severity of AIS is associated with stress response indicators, in particular with the serum cortisol and HbA1c-based glycemic variables we studied, but not in every case with admBG, as well as with inflammatory markers – leukocytes, neutrophils, Neutro/Lympho ratio, CRP, with the relationship with PGRN and TNF-α being particularly interesting. Characteristic seem to be the dependences with the white blood cell indicators, forming, as already mentioned, the so-called “stress leukogram“.

4. Factors associated with glycemic status in patients with acute ischemic stroke

We observed different dynamics of BG in the individual groups according to the glycemic status. In patients with SH, there was a significant decrease in fasting BG from the second day of hospitalization compared to those with known and newly diagnosed T2DM, who in turn maintained significantly higher mean fasting BG values during the hospital stay. These observations support the concept of SH, that it is a transient phenomenon caused by the acute stress

reaction. In connection with the described dynamics of BG, emphasizing precisely the stressful nature of these changes, all three groups showed a significantly greater GV compared to the group of patients with NG when taking into account admBG. However, glucose variability, calculated on the basis of fasting BG in the following days, demonstrated significantly higher values only in patients with known T2DM – a disease characteristic that patients face in the struggle for good glycemic control.

As already noted, SH is associated with a greater severity of AIS, which is also supported by significantly higher serum cortisol levels in these patients. More severe stroke, in turn, is characterized by changes in the white blood cell count, namely a tendency towards leukocytosis, neutrophilia, eosinopenia and lymphopenia.. In this line of thought, our observations on these parameters in the group of patients with SH are logical. The level of leukocytes was the highest in the SH group, we reported significantly higher levels of neutrophils, as well as the Neutro/Lympho ratio, in the SH group compared to the control group. Again, eosinophil and lymphocyte levels were lowest in the SH group, although no significant difference was reached. The results of the correlation analysis were also supportive, demonstrating a positive association of leukocytes, neutrophils, the Neutro/Lympho ratio and a negative one of eosinophils and lymphocytes, not only with admBG, but also with glycemic variables, indicators specifically for SH.

Patients with SH also showed the highest levels of other inflammatory markers such as CRP, which also demonstrated a significant difference compared to the control group with NG. Considering the positive association of the indicator with the severity of AIS, we could explain our observations in the group with SH, given that it is characterized by the highest severity of AIS. In addition, however, CRP showed a correlation not only with admBG and glycemic variables, but also with fasting avBG, which we believe is a reflection of the known deterioration of glycemic control during the course of an infectious process.

Despite the data that PGRN is involved in the regulation of glucose metabolism (Korolczuk A, 2017), and that its serum levels are increased in patients with DM (Youn BS, 2009; Qu H, 2013), we did not find a significant difference in the levels of the indicator in patients with different glycemic status, nor did we report a relationship with any of the glycemic parameters. Similarly, we did not observe a significant difference in TNF-α levels or the PGRN/TNF-α ratio. It is likely that the differences in these parameters between patients with and without DM due to chronic low-grade inflammation are equalized by the acute stroke that occurs and the accompanying acute inflammatory reaction. In support of this statement is the fact that the levels of PGRN, TNF-α and their ratio

are the highest precisely in the group with SH, although they do not reach statistical significance, where, as already reflected, the highest levels of leukocytes and significantly higher levels of neutrophils and CRP are observed compared to the control group with NG.

In contrast to some researchers who found a positive association of GV indicators with inflammatory markers such as TNF-α, IL-6, CRP in AIS (Cai Y, 2022), we observed a negative one between CV 2-4 and TNF-α, but a positive association of all three GV indicators with the PGRN/TNF-α ratio. We could assume that the inflammatory microenvironment reflects not only the level of glycemia, but also its stability during the course of AIS. Age, on the other hand, appeared to be negatively associated with fasting BG variability and insulin level, and also with admBG (in stage I of the study). These results indicate that with increasing age, patients respond with a smaller increase in BG to stressful situations and, in general, BG shows less variation in them, possibly an expression of the decreased reactivity of the older organism. Considering the fact that more than 2/3 of the participants in our study were over 70 years of age, we could explain the lack of correlation of GV indicators with the severity of AIS and outcome measures. At the same time, the insulin level appears to be lower in older patients, which explains the higher incidence of T2DM in the elderly.

Regarding patients with T2DM, both known and newly diagnosed, we quite expectedly reported the highest values of all glycemic parameters compared to the other groups, with the exception of HbA1c-based glycemic variables, which have already been mentioned as dominating the group with SH. Also very characteristic were our observations on the lipid profile, which showed significantly lower levels of HDL-C and higher levels of TG in patients with diabetes compared to those without it. This is supported by the established negative relationship of HDL-C and positive relationship of TG on the one hand with fasting avBG and with HbA1c on the other.

In stage II of our study, there were significantly more women with SH than those with NG and nT2DM. The proportion of women with known T2DM was also higher, although they did not reach a statistically significant difference. Despite the fact that in stage I we did not register significant intergroup differences in gender distribution, in all groups the number of affected women was greater. Overall, in both stages, although without significant difference, we observed a slight female predominance in the total samples.

There is considerable evidence of the disproportionate burden of stroke on women. Results from the Framingham Study show that between the ages of 55 and 75, the lifetime risk of stroke is higher for women, possibly due to their longer life expectancy (Seshadri S, 2007). Smaller studies have examined the change in stroke risk with age by gender and have observed a higher incidence of stroke in

women compared to men under the age of 30, the inverse relationship in adulthood, and a similar or higher incidence in women over the age of 80 (Vyas MV, 2021; Madsen TE, 2020). Similar are our results, which, although not including people under the age of 40, demonstrate a significant predominance of the male gender in the age group below 70 years and of the female gender above this age. The reason for these differences lies in existing gender differences in some of the main RFs for AIS, as well as in the presence of female-specific RFs such as length of reproductive life, use of oral hormonal contraceptives, hormone replacement therapy, etc. Both DM and AH are associated with a higher risk of AIS in women, with this risk increasing in women with lower fasting BG levels and lower SBP compared to men. Additionally, obesity and atrial fibrillation were also more strongly associated with stroke in women.

The significant gender difference in the nT2DM group in favor of men suggests a higher incidence of undiagnosed diabetes in them, possibly the result of insufficient screening and prevention in men. This could be related to lower doctor office attendance in men and insufficient health engagement, but still the patients in this group are too few to draw general conclusions.

Overall, in patients with SH, we observed elevated levels of inflammatory and stress markers, while in those with DM, we reported changes in lipid parameters characteristic of secondary dyslipidemia in this disease, as well as elevated levels of all glycemic parameters, with the exception of glycemic variables based on HbA1c, which are characteristic of SH.

5. Prognostic significance of glycemia in acute ischemic stroke

Regarding the prevalence of fatal outcome, we observed a similar frequency in both stages of the study, namely 25.77% for stage I and 24.56% for stage II, with the proportion of patients with SH also being similar – 26.57% and 28.57% respectively. In stage I, we reported a comparable proportion of patients with a fatal outcome between the groups with SH and T2DM and a significantly lower proportion in the group with NG, while in stage II, the proportion of deceased patients in the group with SH was significantly higher than those with NG and T2DM. Due to the possibility of erroneous inclusion of patients with SH in the group with T2DM in stage I of the study, we have reason to assume that it is SH that is associated with an increased risk of fatal outcome.

The worst functional outcome at discharge was reported in the group with SH, however, demonstrating a difference with borderline significance compared to the other groups. Regarding the severity of AIS at discharge, as well as the

length of hospital stay, we did not observe significant differences between the SH group and the other three groups, although the hospital stay was the longest in the SH group.

In stage I of our study, the levels of admBG were significantly higher in the group of deceased patients compared to those who survived, while in stage II, although the same trend was present, the difference was not reliable. Comparative analysis of glycemic parameters revealed that all of them were higher in the group with deceased patients, but a significant difference was present only with respect to fasting avBG during the course of hospitalization. However, the presence of similar levels of admBG between the group with SH and the groups with DM, while at the same time a significantly higher proportion of patients with fatal outcome among those with SH, speaks in favor of a worse impact of hyperglycemia on admission in patients without DM.

In both I and II stages of the study, admBG did not show a correlation with the fatal outcome and also with the other indicators of the outcome of AIS. In contrast, however, for HbA1c-based glycemic variables, we found a weak positive association with the poor functional stroke outcome of the mSHR and the borderline one of the SHR. Because this association appeared to be dependent on the diabetic status of the patients, we performed a subgroup analysis that demonstrated a clear association of all HbA1c-based glycemic variables with functional outcome, but only in patients without diabetes. These results speak in favor of a prognostic value of glycemic variables, but not of admBG, but only in patients without chronically elevated BG levels.

A number of studies have also found an association of different HbA1c-based glycemic variables with adverse outcomes from AIS, both in terms of functional outcome (Sun Y, 2023; Shi X, 2025) and mortality, short-term (Mi D, 2022) or long-term (Zhu B, 2019; Zhang Y, 2024), and some have also observed an association with prolonged hospital stay (Shen D, 2024) or severity of AIS at discharge (Yang CJ, 2017). And while there is consensus on this relationship in general, there is conflicting data in the literature regarding the impact of SH, particularly glycemic variables, depending on the diabetic status of patients. It seems logical that SH would affect patients without DM more severely, and a number of studies have shown just that (Guo Y, 2021; Duan H, 2023). These observations may be explained by cellular adaptation to hyperglycemia due to physiological readjustments to higher BG levels in patients with diabetes. However, some groups have found an association of SH with adverse outcome independent of diabetes status (Ngiam JN, 2022; Shen D, 2024), while others have found one in a sample composed entirely of people with DM (Yang CJ, 2017; Mi D, 2022). A meta-analysis of 11 cohort studies published early last year concluded that high SHR was associated with worse clinical outcomes after AIS,

suggesting that these results may be more applicable to people without diabetes (Jiang Z, 2024). Meanwhile, another more recent meta-analysis concluded that higher SHR was associated with a higher risk of all-cause mortality in patients with AIS, regardless of diabetes status (Esdaile H, 2024). More data are needed to establish whether the prognostic power of HbA1c-based glycemic variables is dependent on the presence of diabetes.

Regarding admBG as an indicator of SH, of course there are studies that observe increased values in patients with AIS and fatal outcome (Reiche EMV, 2019), as we also reported in stage I of our study. Others additionally find an association with worse prognosis in AIS (Hasan N, 2012). In fact, admBG would be a good indicator and its association with clinical outcome would be more pronounced in a cohort of patients with a narrow HbA1c range. In such a situation, background glycemia would be similar and the absolute value of admBG would more adequately reflect acute glycemic changes. However, in the case of large variations in HbA1c levels, baseline glycemia will also vary widely, and this will lead to a decrease in the significance of admBG as an indicator of SH. For this reason it becomes necessary to use specific markers for SH, such as HbA1c-based glycemic variables.

In our study, we also observed significantly higher mean morning BG values in patients with fatal outcome, specifically in the NG and SH groups. However, correlation analysis showed that fasting avBG was positively associated with fatal outcome and also with poor functional outcome, regardless of diabetic status, other RFs, and patient age. Regression and ROC analyses support the involvement of mean fasting BG levels in predicting mortality risk. With respect to the severity of AIS at discharge, fasting avBG showed a relationship with borderline significance.

In support of our results are the data of a team from China (Mi D, 2017), which found that persistent hyperglycemia during the first 24 hours of AIS onset in patients without DM was associated with an increased risk of death, in contrast to both patients maintaining normoglycemia and those presenting only with hyperglycemia on admission or at the 24th hour. One possible mechanism for this result is the detrimental effect of hyperglycemia on the ischemic penumbra and its potential to increase the size of the ischemic zone. It is known that the penumbral zone remains viable for a period of time, and it is during this period that various factors could have an adverse effect on it. Given the dynamics of the processes that develop in this area, it is logical that not only admBG, but also its subsequent deviations have an impact. Baird et al. (2003) also managed to confirm that persistent hyperglycemia at 72-hour follow-up (represented by both avBG from serial capillary BG measurements and avBG from CGM) was independently associated, including diabetes status, with the expansion of the infarct area, which was associated with a poor clinical outcome. Another possible

mechanism linking persistent hyperglycemia with adverse outcomes after AIS is the increased incidence of hemorrhagic transformation observed in these patients, in contrast to cases with baseline hyperglycemia or hyperglycemia at the 24th hour (Mi D, 2017).

Regarding GV indicators, we did not establish a definitive association with the outcome of AIS, but only a borderline significance of the relationship of CV 1-4 with the severity of AIS at discharge and of ΔBG with the length of hospital stay. Despite the existing data on the association of in-hospital mortality in critical illness with high GV (Egi M, 2006; Hsu CW, 2020), there are few observations in acute stroke. Most of them are focused on longer-term outcomes, showing an independent association of high GV with 3-month mortality (Lin J, 2022). At the same time, Palaiodimou et al. (2021), by using CGM during 96 hours of the stroke, did not reveal a relationship between 13 studied indicators of GV and the 3-month clinical results, and it is appropriate to specify that the mortality at 3 months was not studied, due to a low frequency of cases. However, by also analyzing outcomes within the hospitalization such as in-hospital mortality, neurological improvement or deterioration, they found an independent association of one of the GV indicators, namely mean absolute glucose (MAG), with a lower probability of neurological improvement, as measured by an increase in NIHSS at discharge compared to baseline. The authors discuss a possible shorter-term impact of GV on early neurological status after stroke.

High acute GV appears to have an impact on stroke outcomes, but different ways of defining it, as well as methods of measuring it, undoubtedly affect the statistical analysis. As the most likely reason for our uncertain results, we can point to the small number of BG measurements and the assessment mainly of fasting BG, but not of its diurnal variation. Certainly, assessment of GV parameters using CGM systems would give the most reliable result, but at present, such studies in patients with acute stroke are limited. Another point, with a possible influence on our results, is the already discussed lower variation of BG in older patients, as were the majority of our participants.

In summary, we found indirect evidence of increased mortality risk in patients with SH. We observed an association of HbA1c-based glycemic variables, but not admBG, with poor functional outcome, supporting the proposition that they better identify high-risk patients. As markers that more accurately reflect SH independent of background glycemia, we showed that acute hyperglycemia in critical illness has an adverse effect in patients unaccustomed to chronically elevated glucose levels. Fasting avBG levels were positively correlated with both poor functional outcome and mortality, regardless of the presence of DM. It was also demonstrated that mean fasting BG values during hospitalization significantly predict mortality. These results link persistent

hyperglycemia to adverse outcomes, regardless of the patients' diabetes status. It is likely that GV is associated with an unfavorable stroke outcome, but further studies using CGM systems are needed to confirm.

6. Other factors with prognostic significance in acute ischemic stroke

In both stages of our study, we found that the deceased patients were significantly older than the survivors. In addition, we reported a positive association of age with the fatal outcome, as well as with the functional outcome in the second stage. Given the predominant involvement of older patients with AIS, which is the majority of our patients, as well as the high frequency of comorbidities among them, the number of which also positively correlates with the functional outcome, associations with outcome indicators are expected.

Data from the United States shows that stroke is the fifth leading cause of death in men but the third leading cause of death in women, and this statistic has remained consistent over the years (Heron M, 2021). Some studies report that women have a higher death rate from stroke compared to men (Appelros P, 2009; Thrift AG, 2009), while others report no similar observations (Kapral MK, 2005; Abdu H, 2022). The difference in favor of women is probably due to their usually older age at the onset of stroke, because age-adjusted studies show just the opposite, namely lower mortality in women (Niewada M, 2005; Olsen TS, 2007). In our study, although without statistical significance, the proportion of men was greater among deceased patients regardless of their age. However, we observed a significantly higher proportion of men affected by AIS under the age of 70 years and a higher frequency of female involvement over the age of 70 years. At the same time, we reported higher mortality rates in people over 70 years of age, who also represented the majority of our sample. Despite this distribution, we found similar mortality rates between genders in both age groups. A possible explanation for these observations is precisely the greater survival rate in women compared to men over the age of 70. However, we cannot draw general conclusions regarding people under the age of 70 due to the small number of patients with a fatal outcome.

Among the comorbidities, the incidence of atrial fibrillation and HF was significantly higher in deceased patients compared to survivors. Our subanalysis showed that the increased incidence of atrial fibrillation was at the expense of patients with T2DM. Regarding HF, we observed a higher incidence only in deceased patients with SH compared to survivors. This could be explained by the significant proportion of patients in the group with SH with existing HF as a

concomitant pathology, as well as the significantly higher proportion of deceased patients in this group compared to the others. These two comorbidities are probably of particular importance in patients with AIS, given similar data from other teams (Tziomalos K, 2017; Zhang B, 2020) on their increased incidence in patients with an unfavorable outcome, and a team from Thailand (Krongsut S, 2024) identified them among stroke RFs as being associated with an increased incidence of in-hospital mortality, regardless of diabetes status.

In patients with fatal outcome, we expectedly observed significantly more severe AIS, which positively correlated not only with the fatal outcome, but also with the poor functional outcome, as well as with the severity of AIS at discharge. The length of hospital stay was found to be negatively related to the fatal outcome. Inevitably, the severity of AIS is a leading factor affecting stroke outcome and our results support this thesis - participation in the final reduced model of our regression analysis for predicting death outcome, as well as the largest area under the curve from the ROC analysis specifically for the severity of AIS at admission.

Additionally, in deceased patients, we reported significantly higher levels of cortisol, which, like the severity of AIS at admission, was positively associated with lethal outcome, poor functional outcome, and the severity of AIS at discharge. However, it is likely that cortisol not only correlates with stroke severity but is also independently associated with adverse outcome in these patients, as evidenced by data that prolonged exposure to elevated cortisol levels has a neurotoxic effect (Barugh AJ, 2014). Some studies have found that high cortisol levels independently predict mortality (Anne M, 2007), as well as poor functional outcome (Neidert S, 2011), others have found an association with early mortality within 7 days of stroke onset but not with mortality or poor functional outcome at 3 months (Christensen H, 2004), while others have found no such associations at all (Zierath D, 2011). Our results support the thesis of an independent relationship between cortisol and these indicators, including the severity of AIS, and the regression analysis and the second place in the ROC analysis emphasize its significant role in predicting death outcome.

Of interest are the significantly higher cortisol levels found in women compared to men, which seem to be at the expense of patients with a fatal outcome, since in contrast, no gender differences in cortisol levels were found in patients who survived AIS. At the same time, the tendency for higher cortisol levels in the deceased was present, both in the total sample and in both sexes separately, and the association of cortisol with lethal outcome was independent of the patients' gender. It is possible that the explanation for women demonstrating higher cortisol levels lies in the predominance of the female gender in the group with SH, where mortality is significantly higher compared to

the other groups according to glycemic status, and as already noted, cortisol reaches the highest levels precisely among patients with SH – an expression of a stronger stress reaction and more severe stroke.

Besides the possible neurotoxic effect of hypercortisolemia, its immunosuppressive effect is known to be associated with an increased risk of infections, possibly contributing to the unfavorable outcome in these patients. Our results show a direct correlation of cortisol with the number of leukocytes, neutrophils, as well as with the level of CRP and TNF-α. In addition, we found a positive association with patient age and number of RFs for AIS, which would also contribute to adverse outcome.

In stage I of our study, we observed a significantly higher leukocyte count in deceased patients compared to survivors, as well as a positive relationship between leukocyte levels and mortality. In the II stage, we reported the same trend in the number of leukocytes, although significance was not reached, but we found a direct association with the functional outcome and hospital stay. On the other hand, DBC analysis revealed significantly higher neutrophil counts, lower basophil and lymphocyte counts, and higher Neutro/Lympho ratio values in deceased compared to surviving patients. Correlation analysis showed that neutrophils were positively associated with functional and fatal outcome, eosinophils – negatively with functional outcome, and basophils and lymphocytes, in addition to functional outcome, negatively correlate with lethal outcome. Undoubtedly, white blood cell parameters are involved in the processes that develop in AIS. Zierath et al. (2018) also observed that lymphopenia was associated with worse functional outcome of acute stroke. And for the Neutro/Lympho ratio, which has been widely studied in recent years, a positive relationship with poor functional outcome and mortality in AIS has been reported (Zheng L, 2024; Poyraz T, 2024). Our results also demonstrated a positive association of the Neutro/Lympho ratio with functional outcome and mortality, in contrast to neutrophils, regardless of the severity of AIS at admission. Given the result of the ROC-analysis, as well as the participation of the ratio Neutro/Lympho in the final regression model for predicting death outcome, the role of this indicator as a prognostic marker is emphasized.

The inflammatory marker CRP also demonstrated significant differences between groups according to AIS outcome. It showed a direct association not only with fatal outcome, but also with functional outcome and hospital stay. Other research groups have also found similar relationships between CRP and lethal outcome (Kulaba N, 2024), as well as functional outcome (Alfieri DF, 2020), and a meta-analysis concluded in favor of the routine use of CRP for stratifying the risk of death in patients with AIS, given the observations that elevated levels of the marker are associated with an increased risk of all-cause

mortality in these patients (Yu B, 2019).

Another interesting point observed in both stages of our study were the differences in lipid profile indicators, namely significantly lower levels of total cholesterol and LDL-C in patients with a fatal outcome. In addition, in both stages, the indicators were negatively associated with the fatal outcome, and total cholesterol separately showed a negative relationship with the functional outcome, as the observed dependencies were independent of statin treatment. We could hypothesize that in patients with a fatal outcome associated with higher serum cortisol levels, a reduction in cholesterol levels is observed, given its role as a precursor in cortisol synthesis. However, we did not register a correlation between cortisol and lipid parameters. Another perspective is that of the neuroprotective role of cholesterol, expressed in the promotion of angiogenesis in tissue under hypoxia, a role in the autophagy process in stroke, brain functional recovery, as well as involvement in axon guidance and synapse formation. High plasma levels of total cholesterol and LDL-C are well known as risk factors for atherosclerotic cardiovascular disease. But while their role in coronary heart disease is definitive, their impact on stroke remains controversial and is still under investigation. Total cholesterol and LDL-C may indeed act as a risk factor for cerebrovascular disease but also play an important role in the recovery of brain damage after the onset of stroke. In support of this statement are a number of reports observing on the one hand that high levels of total cholesterol on admission are associated with increased long-term survival after AIS (Markaki I, 2014), and on the other hand that low levels of total cholesterol are associated with worse long-term functional outcome (Zhao W, 2016), those of LDL-C in the recommended range – with low overall survival after AIS (Freitas-Silva M, 2020), and that significantly lower levels of total cholesterol and LDL-C are observed in patients who died during their hospital stay (Zhang B, 2020). Still, not all researchers report such dependencies (Wang H, 2019), which according to Kim et al. (2024) is due to the differential influence of the LDL-C level in the different AIS subtypes. Factors such as stroke recurrence, prevalence of dyslipidemia, its control, in particular statin treatment, are also likely to be important. Based on all of the above, we believe that further studies are needed to unravel the complex relationships between factors associated with lipid parameters, as well as their role in relation to the outcome of AIS.

Additionally, in stage I of our study, we reported significantly higher creatinine levels in patients with a fatal versus favorable outcome, as well as a positive correlation of creatinine with fatal outcome, which was not confirmed in stage II, although we observed the same trend in its level. There we reported a negative association of estimated glomerular filtration rate with poor functional outcome, which, however, disappears after adjustment for the severity of AIS at

admission. Moreover, in stage II of the study, we observed significantly higher urea levels in deceased patients, as well as a positive correlation of its level with functional and lethal outcome, which turned out to be independent of the severity of stroke on admission, despite a similar dependence on outcome indicators. At the same time, our regression analyses showed that urea has a place in predicting the severity of AIS, but not the mortality outcome. It appears that urea has the potential to influence the severity of AIS as well as short-term mortality, but further studies are needed for confirmation.

From the outcome measures, we found that PGRN showed a direct relationship with the severity of AIS at discharge, but not with mortality or functional outcome. However, such observations were made by Xie et al. (2016), but they reported the 6-month outcome of AIS, which undoubtedly matters.

Higher insulin levels have been reported in AIS survivors (Reiche EMV, 2019), as well as in those with better functional outcome (Alfieri DF, 2020), which was not present in our sample.

In conclusion, the most definitive results are from the regression analysis, which distinguishes the severity of AIS on admission, cortisol and fasting avBG as the indicators that statistically significantly predict mortality, as well as from the ROC analysis, which confirms their strongest influence on mortality, but in addition, although with less significance, reveals the influence of the Neutro/Lympho ratio, neutrophil count and CRP.

VI. CONCLUSIONS

1. Glycemic disorders are widespread in patients with AIS, which requires their adequate assessment.
2. HbA1c-based glycemic variables are better determinants of SH than absolute BG values.
3. Stress hyperglycemia occurs more frequently in patients with more severe AIS.
4. Stress hyperglycemia is associated with poor functional outcome of AIS in patients without diabetes and possibly with an increased risk of fatal outcome.
5. Persistent hyperglycemia is associated with poor functional outcome of AIS and fatal outcome regardless of patients' diabetes status.
6. Cortisol levels serve as an adequate assessment of the stress response in AIS.
7. High cortisol levels are independently associated with poor functional outcome and fatal outcome from AIS.
8. High values of the Neutro/Lympho ratio are associated with more severe stroke and demonstrate an independent association with poor functional outcome and fatal outcome from AIS.
9. The marker progranulin has utility in assessing the severity of AIS, but further studies are needed to determine its role in predicting stroke outcome.

VII. CONTRIBUTIONS

Of original character:

1. To the best of our knowledge, for the first time in the country, the prevalence of SH in AIS has been studied and HbA1c-based glycemic variables have been used for its assessment.
2. According to the literature reviewed, this is the first time that HbA1c-based glycemic variables have been compared with cortisol levels in assessing the stress response.
3. For the first time, the marker PGRN was analyzed simultaneously in patients with AIS and different glycemic status.

Of confirmatory character:

1. In our study, we found that HbA1c-based glycemic variables provide a better estimate of SH compared to the absolute value of admBG, which is consistent with most observations worldwide.
2. We confirmed that SH occurs in patients with more severe AIS, and observed higher mortality in the SH group, but we did not establish a direct relationship of SH with mortality.
3. We confirmed the few published observations that PGRN can be used to assess the severity of AIS, but we did not observe an association with prognosis except for the severity of AIS at discharge.

VIII. CONCLUSION

Ischemic stroke is a leading cause of mortality and long-term disability worldwide, and SH often accompanies it. In this sense, the concept of SH is a current problem in everyday clinical practice, including its prognostic significance in individuals with AIS.

The main objective of our study was to look for a relationship between glycemic disorders and outcome in patients with AIS, as well as an association with metabolic and inflammatory markers. First of all, we found that glycemic disorders are widespread in patients with AIS, which requires their adequate assessment. In such an acute illness situation, given the possibility of SH, the absolute value of BG cannot be relied upon to make a diagnosis of DM or detect a prediabetic state. The use of an oral glucose tolerance test in this case would be incorrect, and its conduct in outpatient settings after the condition is under control is often omitted. Acute diseases do not affect the value of HbA1c, therefore in such cases it is a more suitable indicator for assessing the glycemic status of patients.

We consider SH to be a sudden increase in BG levels compared to usual levels in connection with an acute condition that is transient in nature. Given that background BG is important for detecting patients with SH, the use of HbA1c-based glycemic variables is emerging, which we have confirmed to be better determinants of SH compared to the absolute value of BG.

To assess the stress response more precisely, we examined serum cortisol levels and compared them with HbA1c-based glycemic variables and absolute BG values. Analysis of the indicators according to the severity of AIS showed that SH is associated with more severe AIS, and HbA1c-based glycemic variables provide a better assessment of the stress response compared to the absolute value of BG, regardless of the presence of diabetes, and that serum cortisol levels can be used to adequately assess the severity of AIS. In addition to reflecting the stress response, however, we obtained data that high cortisol levels are independently associated with adverse outcomes in patients with AIS. We reported an association of SH with poor functional outcome after AIS in patients without diabetes, although we did not find a direct association with mortality. However, persistent hyperglycemia was associated with poor functional outcome and mortality after AIS regardless of the patients' diabetic status.

Leaving aside the stress response indicators, we observed that the severity of AIS was also associated with inflammatory markers such as leukocytes, neutrophils, Neutro/Lymph ratio and CRP, as well as with the anti-inflammatory marker PGRN. Regarding the Neutro/Lymph ratio, we also reported an

independent association with poor functional outcome and fatal outcome from AIS. We were unable to establish definitive data on the prognostic role of PGRN with respect to stroke outcome, but further studies in this direction would provide an answer to this question.

IX. PUBLICITY

List of publications related to the dissertation:

1. Yaneva Z, Boyadzhieva M, Hristozov K, Tsalta-Mladenov M. Stress hyperglycemia in patients with acute ischemic stroke. *Endocrinologia.* 2018; 3; 151-160.
2. Yaneva Z, Boyadzhieva M. Relative hyperglycemia and HbA1c-based glycemic variables – a literature review. *Varna Medical Forum*. 2022; 11(1); 73-77. doi: 10.14748/vmf.v0i0.8420.
3. Yaneva Z, Boyadzhieva M. Significance of stress hyperglycaemia in acute ischemic stroke – a literature review. *Varna Medical Forum*. 2022; 11(2); 133-139. doi: 10.14748/vmf.v11i2.8578.
4. Yaneva Z, Tsalta-Mladenov M, Bocheva Y, Hristozov K, Boyadzhieva M. Cortisol levels and HbA1c-based glycemic variables for the assessment of stress response in acute stroke. *Scripta Scientifica Medica*. 2023; 55(2). doi: 10.14748/ssm.v55i1.9277.

Participation in scientific forums:

1. Yaneva Z, Boyadzhieva M, Hristozov K. Stress hyperglycemia in patients with acute ischemic stroke. – 11th National Congress of Endocrinology. Plovdiv, October 11-13, 2018, oral presentation – published abstract.
2. Yaneva Z, Boyadzhieva M, Bocheva Y. Relationships between stress hyperglycemia, mortality prevalence and some laboratory parameters in patients with acute ischemic stroke. – IFCC WorldLab Congress, Seoul, June 26-30, 2022, poster session – published abstract.
3. Yaneva Z, Boyadzhieva M. Glycemic disorders in acute ischemic stroke. – Third National Stroke Conference, June 3-4, 2023, MU-Varna – oral presentation.
4. Yaneva Z, Tsalta-Mladenov M, Bocheva Y, Boyadzhieva M. Gluco-metabolic markers for the assessment of stress response in acute stroke. – National Congress of Endocrinology. Plovdiv, October 12-14, 2023, oral presentation – published abstract.

X. SCIENTIFIC PROJECTS RELATED TO THE DISSERTATION

„Glycemia in acute ischemic stroke – prognostic significance and relationship with metabolic and inflammatory markers“ – funded bu the Science Fund of MU – Varna (research project № 19033 from 2019).

The scientific research has been approved for conduct by the Research Ethics Committee at the MU – Varna, protocol № 92 / 02.04.2020.

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