ORIGINAL RESEARCH

Cerebral Thrombolysis in Rural Residents Aged ≥ 80

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Purpose: The proportion of older people in Poland is higher in rural areas than in urban areas. Thus, we aimed to evaluate treatment rate and factors associated with outcome and safety of intravenous thrombolysis (IVT) in rural residents aged ≥80 years admitted to primary stroke centers.

Patients and Methods: This study was a retrospective, observational cohort study of 873 patients treated with recombinant tissue plasminogen activator (rt-PA) in primary stroke centers between February 1, 2009 and December 31, 2017. Among them were 527 rural residents and 231 (26.5%) were ≥80 years of age. The analyses between rural and urban patients aged ≥80 and between rural patients aged <80 and aged ≥80 were performed.

Results: The proportion of patients aged ≥80 treated with rt-PA was comparable in rural and urban residents (27.9% vs 24.3% $p = 0.24$). Rural patients aged ≥80 were also characterized by lower incidence of cardiovascular risk factors and better patients' conditions on admission to hospital. Symptomatic intracerebral hemorrhage rate among ≥80-year-old stroke patients was lower in those living in rural areas than in those living in urban areas (5.4% vs 14.3%, $p = 0.02$); there were no differences regarding mortality and 3-month functional outcome between both populations. The older group of rural patients was characterized by a higher 3-month mortality (28.5% vs 12.6%, $p < 0.001$) and lower functional independence rate (34.0% vs 50.5%, $p < 0.001$) than rural younger patients. Antiplatelet (OR 2.43, 95% CI 1.04–5.66, $p = 0.04$) and anticoagulant therapy before stroke (OR 3.64, 95% CI 1.21–10.99, $p = 0.022$), early ischemic changes in baseline computerized tomograprpahy (OR 2.65, 95% CI 1.03–6.82, $p = 0.043$) were associated with unfavorable outcome; and higher National Institute of Health Stroke Scale score on admission (OR 1.01, 95% CI 1.01–1.20, $p = 0.039$), higher baseline count of white blood cells (OR 1.33, 95% CI 1.10–0.62, $p = 0.003$) were associated with mortality in rural patients over 80.

Conclusion: We suggest that rural patients aged ≥80 may be safely treated with IVT in routine practice. However, lower efficacy and a higher mortality must be considered in former use of Vitamin K antagonist and antiplatelet or high white blood cells count.

Keywords: ischemic stroke, rural patients aged ≥ 80, intravenous thrombolysis, atrial fibrillation, VKA

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Introduction

Benefits arising from the development of modern diagnostic methods and therapies, as well as healthy lifestyle modifications, resulted in lengthened life expectancy. Thus, demographic characteristics in Poland have shifted with expansion in the

oldest-old population. According to information from the Ministry of Health, the highest increase concerned people aged at least 80 and their proportion in Polish population doubled, from just under 2% in 1989 to 4% in 2014.[1]

Due to the aging population, the number of acute ischemic stroke (AIS) strokes in Poland, as worldwide, is increasing.[2,3] In recent years, significant progress of evidence-based care for patients with stroke has resulted in a higher number of specific treatments, including intravenous thrombolysis (IVT) with use of recombinant tissue plasminogen activator (rt-PA) and endovascular procedures.[4–6] With the new recommendations, although with certain restrictions, IVT is allowed in patients over 80.[7–9] The Polish recommendation (2013) listed age restrictions on IVT which still remains the most frequent method of effective stroke treatment despite the introduction of endovascular thrombectomy.[10]

The share of older people in the age structure is higher in rural areas than in urban areas.[11] Sparse studies have previously reported on the safety and efficacy of thrombolytic therapy in patients from rural regions, showing inequalities compared to urban areas.[12–15] However, data regarding specific aspects of IVT therapy in the oldest population are unknown. Thus, we aimed to assess the rate and results of IVT treatment of stroke patients from the rural region in primary stroke units in patients aged ≥80 and to evaluate factors associated with outcome, mortality and presence of hemorrhagic complications (symptomatic intracerebral hemorrhage, SICH).

Patients and Methods
Study Design and Population

This study was a retrospective, two-center, observational cohort study of data collected prospectively from 873 patients consecutively treated with rt-PA at primary stroke centers between 01 February 2009 and 31 December 2017. From this group 527 patients lived in rural areas, and 231 were aged (26.5%) ≥80 years. Recruiting study centers are recognized as stroke units according to the Polish national criteria and international recommendation and are equipped with the proper monitoring and diagnostic facilities.[3,16-19] The Emergency Departments (ED) are staffed 24 hours 7 days a week with both a senior neurologist and a senior radiologist.

The tele-stroke services were unavailable for the rural areas considered in our study.

Computed tomography (CT), magnetic resonance imaging (MRI), angio-CT and angio-MRI are easily available within 24 hours. CT scans or less frequently MRI were performed upon admission to the hospital in order to establish the indication for treatment, between 22 and 36 hours and on the seventh day after IVT. To evaluate the etiology of the stroke, transcranial Doppler (TCD), carotid duplex ultrasonography, Holter electrocardiography (Holter ECG), transthoracic echocardiography (TTE) and in the case of some patients transesophageal echocardiography (TEE) were performed. The severity of stroke symptoms was assessed using the National Institute of Health Stroke Scale (NIHSS).[20] The 90-day stroke outcomes were measured using the modified Rankin scale (mRS).[21] A favorable outcome was defined as an mRS score ≤2 points. In all patients IVT was performed within a regular time window (up to 4.5 hours), five patients who received treatment combined with endovascular intervention were excluded from the analysis.

Hemorrhagic transformation (HT) and SICH rates were assessed according to the ECASS II (European Cooperative Acute Stroke Study II) and III criteria.[22,23]

The ethics committee approved all data of analysis (Ethics Committee of Świętokrzyska Medical Chamber). All patients consented to the treatment method and participation in the study according to the Declaration of Helsinki.

Statistical Analysis

This study was based on a retrospective data analysis. The comparisons between rural and urban patients aged ≥80 and between rural patients aged <80 and aged ≥80 were performed. Data gathering, characteristics, and univariate analysis were performed using Microsoft Excel 2017. Logistic regression was performed with STATISTICA v. 9.1. All continuous variables were tested for a normal distribution and equality of variances. Because of the non-normality of the variables, non-parametric Mann–Whitney U-tests were used to perform the univariate analysis of the continuous variables. Categorical data were compared using chi square tests; p values <0.05 were considered statistically significant. The multivariate analysis was performed using multiple logistic regression models. Factors identified

Table 1 The Clinical Characteristics of the Subgroups of Stroke Patients Treated with iv-Thrombolysis Aged ≥80 Living in Rural and Urban Areas

Variables	Patients Living in Rural Areas	Patients Living in Urban Areas	*p* Value
n (%) 231	147(63,64)	84 (36,36)	—
Demographic data			
Male gender, *n* (%)	44 (29,93)	16 (19,05)	0.069
Baseline mRS 0–2	135 (91.84)	74(88.10)	0.351
Arterial hypertension	**97 (65.99)**	**68 (90.95)**	**0.015**
Coronary heart disease	77 (52.38)	38 (45.24)	0.296
History of heart infarct	**11 (7.48)**	**14 (16.67)**	**0.030**
Atrial fibrillation	86 (58.50)	38 (45.24)	0.051
Diabetes mellitus	38 (25.85)	19 (22.62)	0.583
Renal insufficiency	48 (35.04)	37 (48.68)	0.051
Dyslipidemia	111 (75.510	55 (65.48)	0.103
Smoking	4 (2.72	1 (1.19)	0.441
Prior stroke	17 (11.56)	13 (15.48)	0.394
Prior TIA	**12 (8.16)**	**0**	**0.007**
Antiplatelet therapy before stroke	92 (62.59)	51 (60.71)	0.778
Anticoagulant therapy before stroke	25 (17.01)	8 (9.52)	0.118
Logistic parameters			
Onset to treatment time [min] median (IQR)	156 (134.00–205.00)	160.00 (120.00–182.00)	0.210
Onset to door time [min] median (IQR)	90.00 (60.00–120.00)	90.00 (50.00–114.50)	0.378
Door to treatment time [min] (IQR)	60.00 (45.00–88.00)	65.50 (40.00–99.00)	0.555
Stroke onset time			
Nighttime (20:01–06:59h)	18(13.64)	16(21.62)	0.138
Working days	87(65.91)	46(62.16)	0.590
NIHSS on admission [points] median (IQR)	13.00(9.00–18.00)	12.00(8.80–16.00)	0.066
Arterial blood pressure on admission [mmHg] median (IQR)			
MAP	**103.33 (96.00–114.00)**	**115.00 (100.00–121.00)**	**0.036**
Systolic	80.00 (80.00–95.00)	90.00 (80.00–100.00)	0.056
Diastolic	160.00 (140.00–170.00)	165.00 (150.00–176.00)	0.137
Radiological findings in CT or MR scans at baseline, *n* (%)			
Early ischemic changes	43 (29.25)	25 (29.76)	0.934
Old ischemic changes	67 (45.58)	30 (35.71)	0.144
Laboratory findings before thrombolysis median (IQR)			
Glucose level [mmol/L]	6.68 (5.70–8.80)	6.90 (5.75–8.22)	0.886
Cholesterol level [mmol/L]	4.82 (4.09–5.88)	4.55 (3.90–5.66)	0.200
Hemoglobin level [g/dL]	**13.60 (12.70–14.40)**	**13.10 (11.90–14.10)**	**0.047**
White blood cells [x10^9/L]	7.70 (6.40–9.20)	8.25 (6.90–9.30)	0.149
Creatinine level [μmol/L]	84.00 (71.50–97.00)	88.40 (70.50–111.00)	0.063
Glomerular filtration rate [mL/min/1.73 m^2]°	**64.00 (52.00–79.00)**	**58.00 (41.50–75.00)**	**0.037**
aPTT median (IQR)	27.30 (24.70–30.10)	27.20 (24.75–29.90)	0.833
INR median (IQR)	1.07 (1.00–1.10)	1.03 (1.00–1.10)	0.468
Radiological findings in control CT scans, *n* (%)			
No ischemia	**60 (40.82)**	**22 (26.19)**	**0.025**
Ischemic changes	105 (71.43)	66 (78.57)	0.234
COED	39 (26.53)	29 (34.52)	0.200
Hemorrhagic Transformation‡	**22 (16.06)**	**21 (27.63)**	**0.044**

(*Continued*)

Table 1 (Continued).

Variables	Patients Living in Rural Areas	Patients Living in Urban Areas	*p* Value
Etiological classification, *n* (%)			
Large vessel disease	87 (59.18)	46 (54.76)	0.513
Cardioembolism	30 (20.41)	19 (22.62)	0.692
Lacunar stroke	11 (7.48)	13 (15.48)	0.055
Undetermined etiology	19 (12.93)	6 (7.14)	0.173
mRS 0–2 at three months, n(%)	50 (34.01)	37 (44.05)	0.130
SICH ‡,n	**8 (5.44)**	**12 (14.29)**	**0.021**
3-month mortality, *n* (%)	42 (28.57)	26 (30.95)	0.702

Notes: °According to the MDRD formula; ‡according to the ECASS II criteria. The bold values show the significance of the *p* < 0.05.
Abbreviations: TIA, transient ischemic attack; mRS, modified Rankin Scale; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; INR, international normalized ratio; CT, computed tomography; MCA, middle cerebral artery; COED, cerebral edema; ECASS, European Cooperative Acute Stroke Study; SICH, symptomatic intracerebral hemorrhage; MDRD, Modification Diet for Renal Disease; SD, standard deviation; IQR, interquartile range (Q$_1$–Q$_3$).

in the univariate analysis with a *p* value <0.05 were then examined using a multivariate model.

Results

The proportion of patients aged ≥80 treated with rt-PA did not differ in rural and urban residents (27.9% vs 24.3%, *p* = 0.24, ChiSq 1.4). SICH rate was lower in rural patients over 80 (5.4% vs 14.3%, *p* = 0.02); there were no differences regarding mortality and 3-month functional outcome. The older group of rural patients was characterized by lower incidence of cardiovascular risk factors such as arterial hypertension and previous heart infarct, and better patients conditions on admission to hospital, i.e. lower mean arterial pressure (MAP), higher hemoglobin and glomerular filtration rate (GFR) levels, percentage of normal baseline CT and lower incidence of HT and SICH in patients aged ≥80 living in rural areas. Among subjects aged ≥80 years living in rural areas a higher frequency of prior history of transient ischemic attack (TIA) and lower rate of renal insufficiency were found. They have also showed a trend towards a higher presence of atrial fibrillation (AF) (Table 1).

Univariate analysis showed, that patients aged ≥80 living in rural areas were characterized by lower percentage of male gender, prior stroke and TIA, smoker, COED (cerebral edema) in the control CT, nighttime onset of stroke, lacunar stroke, mRS 0–2 after 3 months from stroke onset, SICH, lower MAP, level of GFR, and higher percentage of AF, renal insufficiency,

anticoagulant therapy before stroke, old ischemic changes in baseline CT, higher median NIHSS on admission, and higher mortality than patients aged <80 (Table 2).

Univariate analysis showed that in group of patients living in rural areas treated with rt-PA AF, prior stroke and TIA, anticoagulant therapy before stroke, ischemic changes and COED in control CT, large vessel disease and SICH, higher median NIHSS, MAP, SBP (systolic blood pressure), lower hemoglobin and GFR level were associated with unfavorable long-term outcome and baseline mRS 0–2 was associated with a lower proportion of unfavorable outcome (mRS 3–5); age ≥89, renal insufficiency, prior TIA, ischemic changes and COED in control CT, large vessel disease, SICH, higher median NIHSS, higher glucose, white blood cells, creatinine and INR (international normalized ratio) level were associated with mortality and shorter median onset-to-door time was associated with lower mortality; and age 80–89 and >89, antiplatelet before stroke, longer onset-to-door time, higher median NIHSS, early ischemic changes in baseline CT, higher cholesterol, white blood cells, INR and lower GFR level, ischemic changes and COED in control CT, large vessel disease and mortality were associated with SICH (Table 3).

In patients living in rural areas, multivariate regression analysis identified prior stroke, anticoagulant therapy before stroke, higher NIHSS on admission, SBP, ischemic changes in control CT and LVD (large vessel disease) as a predictor of unfavorable outcome; age

Table 2 The Clinical Characteristics of the Subgroups of Stroke Patients Treated with iv-Thrombolysis Aged <80 and ≥80 Living in Rural Regions

Variables	Patients Aged <80	Patients Aged ≥80	*p* Value
n (%) 527	380 (72.10)	147 (27.90)	—
Demographic data			
Male gender, *n* (%)	**230 (60.53)**	**44 (29.93)**	**<0.001**
Baseline mRS 0–2	364 (95.79)	135 (91.84)	0.070
Arterial hypertension	273 (71.84)	97 (65.99)	0.187
Coronary heart disease	177 (46.58)	77 (52.38)	0.232
History of heart infarct	49 (12,89)	11 (7.48)	0.079
Atrial fibrillation	**122 (32.11)**	**86 (58.50)**	**<0.001**
Diabetes mellitus	70 (18.42)	38 (25.85)	0.058
Renal insufficiency	**59 (18.44)**	**48 (35.04)**	**<0.001**
Dyslipidemia	308 (81.05)	111 (75.51)	0.157
Smoking	**84 (22.11)**	**4 (2.72)**	**<0.001**
Prior stroke	**80 (21.05)**	**17 (11.56)**	**0.012**
Prior TIA	**66 (17.37)**	**12 (8.16)**	**0.007**
Antiplatelet therapy before stroke	225 (59.21)	92 (62.59)	0.478
Anticoagulant therapy before stroke	**35 (9.21)**	**25 (17.01)**	**0.011**
Logistic parameters			
Onset to treatment time [min] median (IQR)	165.00 (135.00–190.00)	156.00 (134.00–205.00)	0.510
Onset to door time [min] median (IQR)	105.00 (67.50–130.00)	90.00 (60.00–120.00)	0.054
Door to treatment time [min] (IQR)	60.00 (43.50–80.00)	60.00 (45.00–88.00)	0.152
Stroke onset time			
Nighttime (20:01–06:59h)	**66 (22.07)**	**18 (13.64)**	**0.041**
Working days	213 (71.24)	87 (65.91)	0.268
NIHSS on admission [points] median (IQR)	**12.00 (7.00–17.00)**	**13.00 (9.00–18.00)**	**<0.001**
Arterial blood pressure on admission [mmHg] median (IQR)			
MAP	**110.00 (100.00–119.33)**	**103.33 (96.00–114.00)**	**0.028**
Systolic	150.00 (140.00–170.00)	160.00 (140.00–170.00)	0.347
Diastolic	88.00 (80.00–91.00)	80.00 (80.00–95.00)	0.091
Radiological findings in CT or MR scans at baseline, *n* (%)			
Early ischemic changes	135 (35.53)	43 (29.25)	0.172
Old ischemic changes	**132 (34.74)**	**67 (45.58)**	**0.021**
Laboratory findings before thrombolysis median (IQR)			
Glucose level [mmol/L]	6.51 (5.79–7.90)	6.68 (5.70–8.80)	0.427
Cholesterol level [mmol/L]	5.13 (4.21–5.70)	4.82 (4.09–5.88)	0.268
Hemoglobin level [g/dL]	13.80 (12.70–14.80)	13.60 (12.70–14.40)	0.067
White blood cells [x10^9/L]	7.90 (6.90–9.60)	7.70 (6.40–9.20)	0.094
Creatinine level [µmol/L]	83.00 (69.80–91.20)	84.00(71.50–97.00)	0.309
Glomerular filtration rate [mL/min/1.73 m^2]°	**74.00 (54.00–90.50)**	**64.00 (52.00–79.00)**	**0.010**
aPTT median (IQR)	26.60 (24.80–28.80)	27.30 (24.70–30.10)	0.089
INR median (IQR)	1.02 (1.00–1.12)	1.07 (1.00–1.10)	0.282
Radiological findings in control CT scans, *n* (%)			
No ischemia	**109 (26.68)**	**60 (40.82)**	**0.007**
Ischemic changes	286 (75.26)	105 (71.43)	0.367
COED	**172 (45.26)**	**39 (26.53)**	**<0.001**
Hemorrhagic transformation‡	42 (13.13)	22 (16.06)	0.407

(Continued)

Table 2 (Continued).

Variables	Patients Aged <80	Patients Aged ≥80	p Value
Etiological classification, *n*(%)			
Large vessel disease	207 (54.47)	87 (59.18)	0.329
Cardioembolism	8 0(21.05)	30 (20.41)	0.870
Lacunar stroke	**56 (14.74)**	**11 (7.48)**	**0.024**
Undetermined etiology	37 (9.74)	19 (12.93)	0.286
mRS 0–2 at three months, *n* (%)	**192 (50.53)**	**50 (34.01)**	**<0.001**
SICH ‡, *n*	31 (8.16)	8(5.44)	0.285
3-month mortality, *n* (%)	**48 (12.63)**	**4 2(28.57)**	**<0.001**

Notes: °According to the MDRD formula; ‡according to the ECASS II criteria. The bold values show the significance of the *p* < 0.05.
Abbreviations: TIA, transient ischemic attack; mRS, modified Rankin Scale; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; INR, the international normalized ratio; CT, computed tomography; MCA, middle cerebral artery; COED, cerebral edema; ECASS, European Cooperative Acute Stroke Study; SICH, symptomatic intracerebral hemorrhage; MDRD, Modification Diet for Renal Disease; SD, standard deviation; IQR, interquartile range (Q$_1$-Q$_3$).

≥80, higher NIHSS on admission, INR and SICH as a predictor of mortality and early ischemic changes, LVD and mortality as a predictor of SICH. Prior TIA and shorter onset-to-door time were a predictor of lower mortality (Figure 1).

Univariate analysis showed that in a group of patients aged ≥80 living in rural areas, female gender, antiplatelet and anticoagulant therapy before stroke, shorter door-to-treatment time, lower MAP, early ischemic changes in baseline CT, ischemic changes and COED in control CT were associated with unfavorable long-term outcome; higher NIHSS, higher baseline count of white blood cells (WBC) and SICH were associated with mortality and higher NIHSS and mortality were associated with SICH (Table 4).

Multivariate regression analysis confirmed that antiplatelet and anticoagulant therapy before stroke and early ischemic changes in baseline CT were predictors of unfavorable long-term outcome in rural octogenarians. Higher NIHSS score on admission and higher baseline count of white blood cells were predictors of mortality and mortality during 90 days after IVT were associated with SICH (Figure 2).

Discussion

This study reports that rural patients over 80 may be effectively and safely treated with IVT in routine practice. Similarly, the former analysis of randomized studies of patients undergoing IVT from the Cochrane Database showed that participants aged over 80 years benefited equally to those aged under 80 years, particularly if treated within 3 hours from stroke onset. This

analysis was mainly based on the results of the International Stroke Trial 3 (IST-3) in which 53% of participants were aged over 80.[24,25] The beneficial effects of alteplase particularly if given within 3 hours was observed in the Thrombolysis in Elderly Stroke Patients in Italy (TESPI) Trial and the updated meta-analysis showed consistent results with prior estimates. However, all our patients were treated in the time window up to 4.5 hours.[26] Regarding our results, lower efficacy and a higher mortality is to be considered in the presence of oral anticoagulant and antiplatelet therapy prior stroke onset and a high WBC count on admission. The latter finding is to be evaluated in further analysis.

The former result showed lower IVT rate in rural patients.[14] Because our findings were published 10 years ago, they have indicated noticeable improvement in stroke care quality in rural areas. However, there are no publications discussing the outcome and safety issues or IVT in elderly rural populations. Małopolska region, the area from which patients were recruited for this study, is characterized by very diverse environmental conditions. The terrains are varied, from lowlands to highlands, but only some of them are transformed due to industrialization and urbanization. In the region, there are no highways or expressways in the region, air transport for stroke patients was practically not used. The furthest village from which patients were delivered is located 72 km from the stroke center.

We did not observe differences between rural and urban population over 80 in terms of long-term outcome and mortality. The CANSEART Stroke Study

Table 3 Univariate Analysis Showing Factors Associated with Unfavorable Outcome (mRS 3–5), 3-Month Mortality and SICH in Patients Living in Rural Areas

Variables	mRS 0–2	mRS 3–5	p Value	Survivors	Patients Who Died	p Value	Without SICH	With ICH	p Value
n (%) 527	332 (63.00)	195 (37.00)	—	437 (82.92)	90 (17.08)	—	488 (92.60)	39 7.40	—
Demographic data									
Male gender, n (%)	167 (50.30)	107 (54.87)	0.310	235 (53.78)	39 (43.33)	0.070	253 (51.84)	21 (53.85)	0.810
Octogenarian (80–89)	75 (22.59)	50 (25.64)	0.427	97 (22.20)	28 (31.11)	0.070	121 (24.80)	4 (10.26)	**0.040**
Nonagenarian (>89)	17 (5.12)	5 (2.56)	0.157	8 (1.83)	14 (15.56)	**<0.001**	18 (3.69)	4 (10.26)	**0.048**
Risk factors, n (%)									
Baseline mRS 0–2	320 (96.39)	179 (91.79)	**0.023**	419 (9.88)	80 (88.89)	**0.007**	463 (94.88)	36 (92.31)	0.491
Arterial hypertension	243 (73.19)	127 (65.13)	0.051	310 (70.94)	60 (66.67)	0.420	34 5(70.70)	25 (64.10)	0.386
Coronary heart disease	161 (48.49)	93 (47.69)	0.859	210 (48.05)	44 (48.89)	0.885	238 (48.77)	16 (41.03)	0.352
History of heart infarct	38 (11.45)	22 (11.28)	0.954	48 (10.98)	12 (13.33)	0.522	54 (11.07)	6 (15.38)	0.414
Atrial fibrillation	118 (35.54)	90 (46.15)	**0.016**	165 (37.76)	43 (47.78)	0.076	192 (39.34)	16 (41.03)	0.836
Diabetes mellitus	70 (21.08)	38 (19.49)	0.661	86 (19.68)	22 (24.44)	0.307	102 (20.90)	6 (15.38)	0.411
Renal insufficiency	72 (23.76)	35 (22.73)	0.805	72 (19.62)	35 (38.89)	**<0.001**	9 9(22.86)	8(33.33)	0.238
Dyslipidemia	259 (78.01)	160 (82.05)	0.267	347 (79.41)	72 (80.00)	0.899	389 (79.71)	3 0(76.92)	0.678
Smoking	64 (19.28)	24 (12.31)	**0.038**	72 (16.48)	16 (17.78)	0.763	80 (16.39)	8(20.51)	0.507
Prior stroke	43 (12.95)	54 (27.69)	**<0.001**	86 (19.68)	11 (12.22)	0.096	91 (18.65)	(15.38)	0.613
Prior TIA	36 (10.84)	42 (21.54)	**0.001**	74 (1.93)	4 (4.44)	**0.002**	69 (14.14)	9 (23.08)	0.130
Antiplatelet therapy before stroke	193 (58.13)	124 (63.59)	0.217	262 (59.95)	55 (61.11)	0.838	287 (58.81)	30 (76.92)	**0.026**
Anticoagulant therapy before stroke	25 (7.53)	35 (17.95)	**<0.001**	48 (10.98)	12 (13.33)	0.522	52 (10.66)	8 (20.51)	0.062
Logistic parameters									
Onset to treatment time [min] median (IQR)	165.00 (134.50–200.00)	165.00 (140.00–190.00)	0.761	165.00 (140.00–190.00)	150.00 (120.00–180.00)	**0.018**	164.00 (135.00–195.00)	175.00 (140.00–190.00)	0.385
Onset to door time [min] median (IQR)	90.0 (60.00–125.00)	100.00 (75.00–129.00)	0.112	100.00 (71.00–130.00)	75.00 (50.00–120.00)	**<0.001**	95.00 (65.00–121.50)	130.00 (70.00–130.00)	**0.013**
Door to treatment time [min] (IQR)	60.00 (43.50–85.00)	60.0 0(45.00–70.00)	0.087	60.00 (45.00–80.00)	60.00 (35.00–90.00)	0.595	60.00 (45.00–80.50)	60.00 (40.00–60.00)	0.228
Stroke onset time:									
Daytime (07:00–20:00h)	235 (80.2)	112 (81.16)	0.815	276 (80.94)	71 (78.89)	0.662	330 (80.10)	1 7(89.47)	0.313
Nighttime (20:01–06:59h)	58 (19.80)	2 6(18.84)	0.815	65 (19.06)	19 (21.11)	0.662	82 (19.90)	2 (10.53)	0.313
Working days	203 (69.28)	97 (70.29)	0.832	236 (69.21)	64 (71.11)	0.727	286 (69.42)	14 (73.68)	0.692
NIHSS on admission [points] median (IQR)	11.00 (7.00–16.00)	14.00 (11.00–18.00)	**<0.001**	11.00 (7.00–16.00)	18.00 (12.00–20.00)	**<0.001**	12.00 (8.00–17.00)	14.00 (11.00–20.00)	**0.001**
Arterial blood pressure on admission [mmHg] median (IQR)									
MAP	106.67 (98.33–116.00)	110.00 (96.67–120.00)	0.127	106.67 (96.67–118.67)	107.33 (100.00–116.67)	0.941	106.67 (96.67–117.17)	116.00 (106.67–121.83)	0.051

(Continued)

Table 3 (Continued).

Variables	mRS 0-2	mRS 3-5	p Value	Survivors	Patients Who Died	p Value	Without SICH	With ICH	p Value
Systolic	150.00 (136.00-170.00)	160.00 (140.00-170.00)	0.014	150.00 (140.00-170.00)	160.00 (140.00-170.00)	0.681	150.00 (140.00-170.00)	146.00 (140.00-170.00)	0.429
Diastolic	85.00 (80.00-93.00)	88.00 (80.00-93.00)	0.549	87.00 (80.00-95.00)	84.00 (80.00-90.00)	0.479	85.00 (80.00-93.00)	90.00 (80.00-95.00)	0.132
Baseline radiological findings in CT or MR scans, n (%)									
Early ischemic changes	102 (30.72)	76 (38.97)	0.053	151 (35.55)	27 (30.00)	0.405	152 (31.15)	26 (66.67)	<0.001
Old ischemic changes	115 (34.64)	84 (43.08)	0.054	165 (37.76)	34 (37.78)	0.997	181 (37.09)	18 (46.15)	0.261
Laboratory findings before thrombolysis median (IQR)									
Glucose level [mmol/L]	6.60 (5.62-8.30)	6.50 (5.80-7.70)	0.838	6.49 (5.70-7.90)	7.34 (6.00-8.90)	0.009	6.60 (5.70-8.26)	6.50 (5.80-7.20)	0.366
Cholesterol level [mmol/L]	5.03 (4.16-5.70)	5.24 (4.13-5.88)	0.645	5.12 (4.16-5.85)	4.75 (4.00-5.70)	0.136	5.03 (4.14-5.70)	5.80 (3.92-6.44)	0.019
Hemoglobin level [g/dL]	13.90 (12.90-14.90)	13.50 (12.60-14.20)	<0.001	13.80 (12.60-14.60)	13.85 (12.90-15.00)	0.296	13.80 (12.70-14.75)	13.20 (12.90-14.50)	0.406
White blood cells [x10^9/L]	7.90 (6.60-9.80)	7.70 (6.90-9.30)	0.516	7.70 (6.75-9.30)	8.80 (6.70-10.70)	0.011	7.70 (6.60-9.30)	9.40 (7.90-11.20)	<0.001
Creatinine level [μmol/L]	82.60 (69.00-95.00)	84.20 (71.00-91.00)	0.473	83.00 (69.80-91.00)	85.50 (71.00-107.00)	0.044	83.00 (69.80-92.55)	88.40 (83.00-91.20)	0.067
Glomerular filtration rate [mL/min/1.73 m^2]°	71.50 (56.00-89.50)	68.00 (41.00-86.00)	0.013	71.00 (52.00-89.00)	65.00 (54.00-86.00)	0.592	71.00 (55.00-89.00)	55.00 (10.00-78.00)	<0.001
aPTT median (IQR)	26.70 (24.60-29.00)	27.10 (25.00-29.10)	0.158	26.80 (24.80-29.20)	26.75 (24.55-28.80)	0.553	26.70 (24.70-29.20)	28.20 (26.60-28.80)	0.116
INR median (IQR)	1.02 (1.00-1.12)	1.04 (1.00-1.10)	0.361	1.02 (1.00-1.10)	1.09 (1.00-1.17)	0.045	1.02 (1.00-1.10)	1.14 (1.00-1.23)	<0.001
Radiological findings in control CT scans, n (%)									
No ischemia	123 (37.05)	46 (23.59)	0.001	162 (37.07)	7 (7.78)	<0.001	164 (33.61)	5 (12.82)	0.007
Ischemic changes	218 (65.66)	173 (88.72)	<0.001	316 (72.31)	75 (83.33)	0.029	352 (71.13)	39 (100.00)	<0.001
COED	108 (32.53)	103 (52.82)	<0.001	166 (37.99)	45 (50.00)	0.034	181 (37.09)	30 (76.92)	<0.001
Hemorrhagic transformation‡	41 (13.53)	23 (14.94)	0.683	40 (10.90)	24 (26.67)	<0.001	45 (19.39)	19 (79.17)	<0.001
Etiological classification, n(%)									
Large vessel disease	168 (50.60)	126 (64.62)	0.002	235 (53.78)	59 (65.56)	0.040	262 (53.69)	32 (82.05)	<0.001
Cardioembolism	67 (20.18)	43 (22.05)	0.610	90 (20.59)	20 (22.22)	0.729	104 (21.31)	6 (15.38)	0.381
Lacunar stroke	59 (17.77)	8 (4.10)	<0.005	65 (14.87)	2 (2.22)	0.001	67 (13.73)	0	0.013
Undetermined etiology	38 (11.45)	18 (9.23)	0.426	47 (10.76)	9 (10.00)	0.832	55 (11.27)	1 (2.56)	0.089
mRS 0-2 at three months, n(%)	—	—	—	—	—	—	214 (49.39)	1 (2.56)	<0.001
SICH ‡, n(%)	18 (5.42)	21 (10.77)	0.023	22 (5.03)	17 (18.89)	<0.001	—	—	—
3-month mortality	—	—	—	—	—	—	73 (14.96)	17 (43.59)	<0.001

Notes: °According to the MDRD formula; ‡according to the ECASS II criteria. The bold values show the significance of the p < 0.05.
Abbreviations: TIA, transient ischemic attack; mRS, modified Rankin Scale; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; INR, the international normalized ratio; CT, computed tomography; MCA, middle cerebral artery; COED, cerebral edema; ECASS, European Cooperative Acute Stroke Study; SICH, symptomatic intracerebral hemorrhage; MDRD, Modification Diet for Renal Disease; SD, standard deviation; IQR, interquartile range (Q_1–Q_3).
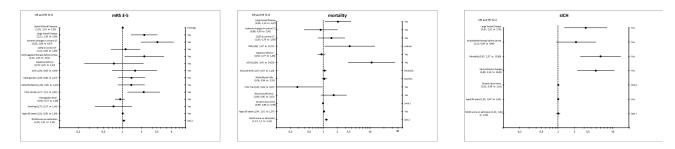
Figure 1 Multivariate logistic regression models showing factors associated with 90 days unfavorable outcome, 3-month mortality and SICH in patients treated with iv-thrombolysis living in rural areas.
Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; COED, cerebral edema; SICH, symptomatic intracerebral hemorrhage; OR, odds ratio; CI, confidence interval.

showed that stroke mortality is higher in rural than in urban areas. The authors reckon that the reason is of higher stroke incidence in rural areas rather than stroke care.[27] As the results of other studies showed, among high HDI (Human Development Index) countries, stroke mortality was higher in rural than in urban areas in contrast to countries with low HDI in which mortality was higher in the cities.[28]

Previous studies showed that in many countries, the population living in rural areas is older than in urban areas, which is related to the migration of working-age people to cities.[29–31] Our analysis showed that population of patients aged ≥80 living in rural areas characterized by lower incidence of cardiovascular risk factors. Cardiovascular risk factors are slightly different in the rural population than in the urban population;[32–34] however, we did not have data for older people. Rural risk factors for health disparities include some kind of geographic isolation, lower socioeconomic status, higher rates of health behaviors, limited access to healthcare specialist, and limited job opportunities.[35] Health care for patients from rural and urban areas is different. As shown by a survey conducted in the United States, rural health priorities have changed little in the last decade and access to health care continues to be the most frequently identified health priority.[36] The prevalence of cardiovascular risk factors, including arterial hypertension and smoking, in various regions of Poland was mostly explained by varying degrees of urbanization.[37]

In the population of patients from Peru, hypertension was more prevalent among the urban (29%) compared to the rural group (11%).[35] The result of the PURE study showed that in urban communities the awareness, treatment, and control of hypertension

were higher compared with rural ones.[37] Płaszkiewicz et al have found that in south-eastern Poland between 1997 and 2009 year the number of rural patients with high blood pressure decreased by nearly a half.[33] Contrary to the results of the studies presented above, the results of a study by Lindroth et al indicate that residents of rural areas were more often treated for hypertension and hyperlipidemia, hospitalized for myocardial infarction and diagnosed with diabetes; however, after adjusting for age and gender there were no differences.[29] An increase of 30% in the prevalence of hypertension in rural populations between 1991 and 2011 was also confirmed by a Chinese study.[38]

Our results showed the connection between an unfavorable outcome and a finding of early ischemic changes in baseline CT. The presence of early ischemic changes in CT remains one of the questionable inclusion/exclusion criteria for IVT.[39] To date, we do not have had clear criteria for assessing early ischemic changes, and in previous randomized trials different criteria were used. Topographic assessment of acute ischemic changes using Alberta Stroke Program Early Computed Tomography Score (ASPECTS) can predict disability, death in anterior circulation stroke and risk of developing SICH.[40] Zou at al indicated that diagnosis of hyperdense middle cerebral artery sign is associated with increased risk of HT after IVT but not with SICH.[41] A recently published study by Tanaka et al showed that the detection of early ischemic changes using ASPECTS in CT (CT-ASPECT) and in MRI with sequence diffusion weight imaging (DWI-ASPECT) predict SICH in patients with AIS in anterior circulation receiving IVT, but our data did not show such correlation.[42]

In contrast to previous findings, the impact of antiplatelet and anticoagulant therapy before stroke on unfavorable outcome in analyzed patients was found. Age should not be

Table 4 Univariate Analysis Showing Factors Associated with Unfavorable Outcome (mRS 3–5), 3-Months Mortality and sICH in Patients Aged ≥80 Living in Rural Areas

Variables	mRS 0–2	mRS 3–5	p Value	Survivors	Patients Who Died	p Value	Without SICH	With SICH	p Value
n (%) 147	92 (62.58)	55 (37.42)	—	105 (71.43)	42 (28.57)	—	139 (94.56)	8 (5.44)	—
Demographic data									
Male gender, n (%)	33 (35.87)	11 (20.00)	0.042	32 (30.48)	12 (28.57)	0.820	42 (30.22)	2 (25.00)	0.754
Risk factors, n (%)									
Baseline mRS 0–2	86 (93.0.48)	49 (89.09)	0.347	99 (94.29)	36 (85.71)	0.086	129 (92.81)	6 (75.00)	0.074
Arterial hypertension	66 (71.74)	31 (56.36)	0.057	70 (66.67)	27 (64.29)	0.783	94 (67.63)	3 (37.50)	0.080
Coronary heart disease	48 (51.17)	29 (52.73)	0.948	54 (51.43)	23 (54.76)	0.715	74 (53.24)	3 (37.50)	0.386
History of heart infarct	8 (8.70)	3 (5.45)	0.470	6 (5.71)	5 (11.90)	0.198	11 (7.91)	0	0.408
Atrial fibrillation	50 (54.35)	36 (65.45)	0.186	60 (57.14)	26 (61.90)	0.596	81 (58.27)	5 (62.50)	0.813
Diabetes mellitus	19 (20.65)	19 (34.55)	0.063	25 (23.81)	13 (30.95)	0.371	35 (25.18)	3 (37.50)	0.438
Renal insufficiency	33 (36.67)	15 (31.91)	0.580	29 (30.53)	19 (45.24)	0.096	43 (33.33)	5 (62.50)	0.093
Dyslipidemia	70 (76.09)	41 (74.55)	0.833	78 (74.29)	33 (78.57)	0.585	104 (74.82)	(87.50)	0.417
Smoking	3 (3.26)	1 (1.82)	0.603	2 (1.90)	2 (4.76)	0.336	4 (2.88)	0	0.627
Prior stroke	10 (10.87)	7 (12.73)	0.733	15 (14.29)	2 (4.76)	0.103	17 (12.23)	0	0.293
Prior TIA	7 (7.61)	5 (9.09)	0.751	10 (9.52)	2 (4.76)	0.341	12 (8.63)	0	0.385
Antiplatelet therapy before stroke	52 (56.52)	40 (72.73)	0.049	66 (62.86)	26 (61.90)	0.914	87 (62.59)	5 (6250)	0.996
Anticoagulant therapy before stroke	9 (9.78)	16 (29.09)	0.002	20 (19.05)	5 (11.90)	0.298	24 (17.27)	1 (12.50)	0.727
Logistic parameters:									
Onset to treatment time [min.] median (IQR)	162.50 (130.00–210.00)	155.00 (140.00–180.00	0.522	156.00 (135.00–200.00)	155.00 (120.00–210.00)	0.725	156.00 (135.00–205.00)	160.00 (102.50–175.00)	0.535
Onset to door time [min.] median (IQR)	86.50 (60.00–125.00)	90.00 (65.00–120.00)	0.844	90.00 (68.00–123.00)	77.50 (55.00–120.00)	0.219	90.00 (60.00–120.00)	59.50 (52.50–127.50)	0.374
Door to treatment time [min.] (IQR)	65.5 0(47.00–90.50)	50.00 (45.00–80.00)	0.043	60.00 (49.00–85.00)	75.00 (40.00–95.00)	0.323	60.00 (46.00–88.00)	53.00 (40.00–77.50)	0.567
Stroke onset time:									
Daytime (07:00–20:00h)	78 (87.64)	36 (83.72)	0.538	77 (85.56)	37 (88.10)	0.692	107 (86.29)	7 (87.50)	0.923
Nighttime (20:01–06:59h)	11 (12.36)	7 (16.28)	0.538	13 (14.44)	5 (11.90)	0.692	17 (13.71)	1 (12.50)	0923
Working days	55 (61.80)	32 (74.42)	0.152	57 (63.33)	30 (71.43)	0.361	81 (65.32)	6 (75.00)	0.576
NIHSS on admission [points] median (IQR)	13.00 (8.00–19.00)	15.00 (10.00–18.00)	0.595	12.00 (9.00–18.00)	18.50 (12.00–22.00)	<0.001	13.00 (9.00–18.00)	20.00 (13.50–21.00)	**0.017**
Arterial blood pressure on admission [mmHg] median (IQR)									
MAP	105.00 (100.00–114.00)	96.00 (96.00–110.00)	0.048	100.00 (96.00–114.00)	106.67 (100.00–114.00)	0.674	101.67 (96.00–113.83)	108.00 (103.33–115.00)	0358
Systolic	160.00 (140.00–170.00)	160.00 (130.00–170.00)	0.983	160.00 (140.00–173.00)	152.00 (140.00–160.00)	0.222	160.00 (140.00–170.00)	146.00 (130.00–180.00)	0.773
Diastolic	84.00 (80.00–98.00)	80.00 (80.00–94.00)	0.634	80.00 (80.00–97.00)	86.50 (80.00–91.00)	0.566	80.00 (80.00–96.00)	89.00 (80.00–90.00)	0.963

Baseline radiological findings in CT or MR scans, n (%)								
Early ischemic changes	**20 (21.74)**	**0.010**	35 (33.33)	8 (19.05)	0.085	41 (29.50)	2 (25.00)	0.786
Old ischemic changes	**36 (39.13)**	**0.042**	53 (50.48)	14 (33.33)	0.059	63 (45.52)	4 (50.00)	0.796
Laboratory findings before thrombolysis median (IQR)								
Glucose level [mmol/L]	6.55 (5.61–8.35)	0.239	6.40 (5.70–8.70)	7.60 (6.00–8.93)	0.111	6.61 (5.70–8.80)	7.60 (6.20–9.05)	0.588
Cholesterol level [mmol/L]	4.71 (4.09–5.58)	0.300	4.82 (4.09–5.88)	4.83 (4.09–5.76)	0.847	4.82 (4.09–5.88)	5.23 (4.12–5.38)	0.824
Hemoglobin level [g/dL]	13.55 (12.90–14.50)	0.542	13.60 (12.70–14.20)	13.65 (12.70–14.90)	0.635	13.60 (12.60–14.40)	13.75 (12.95–14.65)	0758
White blood cells [$\times 10^9$/L]	7.60 (6.40–9.55)	0.857	**7.40 (6.40–8.70)**	**8.65 (6.50–11.00)**	**0.004**	7.60 (6.40–9.10)	9.35 (7.65–11.20)	0050
Creatinine level [µmol/L]	83.65 (71.50–103.50)	0.336	83.30 (71.50–92.20)	89.00 (72.00–116.80)	0.073	83.70 (71.50–95.50)	107.55 (80.80–154.00)	0.052
Glomerular filtration rate [mL/min/1.73 m²]°	65.00 (53.00–78.00)	0.531	65.00 (52.00–82.00)	62.00 (52.00–74.00)	0.259	65.00 (52.00–80.00)	56.50 (30.50–66.50)	0.165
aPTT median (IQR)	27.10 (24.70–29.55)	0.229	27.80 (24.80–31.70)	26.35 (24.60–28.80)	0.088	27.40 (24.70–31.00)	25.60 (24.65–28.05)	0.263
INR median (IQR)	1.05 (1.00–1.10)	0.861	1.07 (1.00–1.10)	1.09 (1.00–1.18)	0.252	1.07 (1.00–1.10)	1.00 (0.91–1.14)	0.246
Radiological findings in control CT scans, n (%)								
No ischemia	33 (35.87)	0.115	**55 (52.38)**	**5 (11.90)**	**<0.001**	**60 (43.17)**	0	**0.016**
Ischemic changes	**58 (63.04)**	**0.004**	72 (68.57)	33 (78.57)	0.225	97 (69.78)	8 (100.00)	0.065
COED	**18 (19.57)**	**0.013**	24 (22.86)	15 (35.71)	0.111	35 (25.18)	5 (50.00)	0.122
Hemorrhagic transformation‡	15 (16.67)	0.788	12 (12.63)	10 (23.81)	0.100	–	–	–
Etiological classification, n (%)								
Large vessel disease	58 (63.04)	0.218	57 (54.29)	30 (71.43)	0.056	82 (58.99)	5 (62.50)	0.844
Cardioembolism	17 (18.48)	0.453	21 (20.00)	9 (21.43)	0.846	28 (20.14)	2 (25.00)	0.740
Lacunar stroke	7 (7.61)	0.940	**11 (10.48)**	**0**	**0.029**	11 (7.91)	0	0.408
Undetermined etiology	10 (10.87)	0.337	16 (15.24)	3 (7.14)	0.186	18 (12.95)	1 (12.50)	0.970
mRS 0–2 at three months, n (%)	–	–	–	–	–	**50 (35.97)**	**0**	**0.037**
SICH‡, n (%)	7 (7.61)–	0.134–	1 (0.95)–	7 (16.67)–	<0.001–	37 (25.18)	7 (87.50)	<0.001
3-month mortality								

Notes: °According to the MDRD formula; ‡according to the ECASS II criteria. The bold values show the significance of the p < 0.05.
Abbreviations: TIA, transient ischemic attack; mRS, modified Rankin Scale; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; INR, the international normalized ratio; CT, computed tomography; MCA, middle cerebral artery; COED, cerebral edema; ECASS, European Cooperative Acute Stroke Study; SICH, symptomatic intracerebral hemorrhage; MDRD, Modification Diet for Renal Disease; SD, standard deviation; IQR, interquartile range (Q_1–Q_3).
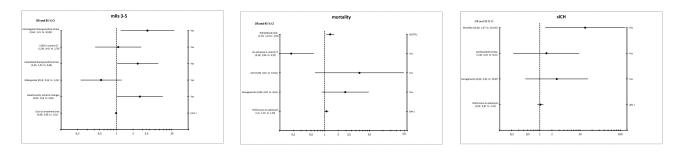
Figure 2 Multivariate logistic regression models showing factors associated with 90 days unfavorable outcome, 3-month mortality and SICH in patients aged ≥80 treated with iv-thrombolysis living in rural areas.
Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; CT, computed tomography; COED, cerebral edema; sICH, symptomatic intracerebral hemorrhage; OR, odds ratio; CI, cConfidence interval.

considered a barrier for implementation of optimal secondary prevention interventions. The available evidence supports benefit from secondary preventive cardiovascular events in the elderly.[43] Antiplatelets impair thrombocyte function and might, therefore, increase the risk of SICH in patients undergoing IVT and despite this, the benefit of IVT for AIS is greater in patients using antiplatelets before stroke.[44,45] Treatment with antiplatelets is not a contraindication to IVT; however, this does not concern the oldest but all treated patients.[46] IVT is allowed for AIS patients on Vitamin K antagonist (VKA) with INR ≤1.7. Literature data suggest that the course of acute-phase cardiogenic stroke and long-term prognosis is more favorable in patients taking oral anticoagulant.[47]

Octogenarians living in rural areas had a higher incidence of AF compared to patients living in urban areas or younger patients living in rural areas, respectively. However, despite the fact that patients in rural areas had a higher incidence of AF, they had a higher percentage of large vessel occlusions and territorial strokes. That may be explained by the fact, that within the recruitment period, the vast majority of patients used warfarin, as novel oral anticoagulants (NOAC) were not reimbursed by the insurer for AF prophylaxis. Additionally, in all patients qualified for treatment with rt-PA the value of the INR was non-therapeutic (≤1.7). Probably, anticoagulant therapy with warfarin was poorly managed in patients living in rural areas, in terms of adequate monitoring of INR due to logistic reasons: no possibilities to reach the laboratory, unavailable system for collecting blood tests in the patient's home. This is in line with previous reports showing that residency in rural areas was one of the strongest predictors of uncontrolled anticoagulation and indicated the logistical difficulties of systematically controlling of INR in a rural environment.[48–50] In our opinion, this is also a reason why a prior anticoagulant therapy was found as an independent predictor of unfavorable outcome in our cohort of rural patients, including octogenarians. A higher frequency of AF without effective anticoagulation among rural patients from our study group can also explain why they tended toward more severe strokes in terms of baseline NIHSS despite the lower incidence of other cardiovascular risk factors and, apparently, better baseline health status than in the urban counterpart. Similarly, the high NIHSS score in rural patients was indicated in previous studies.[51–55]

One should be aware that prognosis for elderly patients is less favorable than for younger patients because observational studies suggest slightly higher incidence of SICH.[56] Therefore, most of the expert groups' guidelines recommend caution in the use of rt-PA in patients over 80.

In many studies, including ours, the connection between high baseline NIHSS, high WBC count and mortality has been shown. The severity of the neurological syndrome is the most important factor referring to both the chance of survival and functional status in long-term observation.[57] Patients with severe stroke were burdened with much higher risk and worse prognosis than lighter patients.[58] Also, previous studies indicated that elevated WBC counts in patients treated with rt-PA predict poor long-term outcome.[59]

The present study has some limitation. This was an observational study and the group of analyzed patients was not large. Although the data collection was conducted in a prospective study, the analysis was retrospective. The study population was limited to two primary stroke centers and was recruited in anon-industrial area. We did not compare it to industrial populations. Thus, we realize that prospective studies are warranted to evaluate the studied clinical issue due to its growing importance.

Based on our results, we suggest that rural patients aged ≥80 may be safely treated with IVT in routine practice. However, especially in patients who use VKA and

antiplatelet therapy, with baseline high NIHSS and with high WBC count, it should be carefully considered, in terms of lower efficacy and higher rate of complications. We believe that our findings provide a certain benefit to the assessment of safety of IVT in elderly patients.

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Disclosure

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