Wake-up stroke: thrombolysis reduces ischemic lesion volume and neurological deficit

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Abstract

Backgrounds Wake-Up Stroke (WUS) patients are generally excluded from thrombolytic therapy (rTPA) due to the unknown time of stroke onset. This study aimed to investigate the effects of rTPA in WUS patients during every day clinical scenarios, by measuring ischemic lesion volume and functional outcomes compared to non-treated WUS patients.

Methods We retrospectively analyzed clinical and imaging data of 149 (75 rTPA; 74 non-rTPA) patients with acute ischemic WUS. Ischemic volume was calculated on follow-up CT and functional outcomes were the NIHSS and mRS comparing rTPA and non-rTPA WUS. Patients were selected using ASPECTS > 6 on CT and/or ischemic penumbra > 50% of hypoperfused tissue on CTP.

Results A reduced volume was measured on the follow-up CT for rTPA (1 mL, 0–8) compared to the non-rTPA patients (10 mL, 0–40; $p = 0.000$). NIHSS at 7 days from admission was significantly lower in the rTPA (1, 0–4) compared to non-rTPA group (3, 1–9; $p = 0.015$), as was the percentage of improvement (ΔNIHSS) (70% vs 50%; $p = 0.002$). A higher prevalence of mRS 0–2 was observed in the rTPA compared to the non-rTPA (54% vs 39%; $p = 0.060$). Multivariate analysis showed that NIHSS at baseline and rTPA treatment are significant predictors of good outcome both in terms of NIHSS at 7 days and ischemic lesion volume on follow-up CT ($p < 0.05$).

Conclusions rTPA in WUS patients selected with CT and/or CTP resulted in reduced ischemic infarct volume on follow-up CT and better functional outcome without increment of intracranial hemorrhages and in-hospital mortality.

Keywords Wake-up stroke · Thrombolysis · Ischemic volume lesion · Neuroimaging · Decision-making

Introduction

Stroke is a neurological condition which may implicate considerable motor and cognitive deficits, and it may be treatable with reperfusion treatments. Between 8 and 28% of ischemic strokes occur during sleep (wake-up stroke—WUS) [1–3]. The time when patients were last known well is used as a time reference for the stroke onset, frequently exceeding the allowed time window for acute stroke treatment. As a result, a considerable portion of WUS patients are generally excluded from thrombolytic therapy due to the unknown time of stroke onset [4, 5]. Circadian variation in the ischemic stroke onset, similar to acute myocardial infarction, has been supposed with a higher frequency in the morning hours [6]. The incidence of early morning strokes incidence is about 50% higher than nighttime [7, 8], probably due to the increase in sympathetic activity, blood pressure, increase in platelet aggregation, and peak in prothrombotic factors and endothelial dysfunction in the early morning [9–11].

The WAKEUP trial demonstrated the benefit of intravenous thrombolysis with alteplase in patients with stroke symptoms on waking by identifying an MRI pattern

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suggestive of stroke with an onset of less than 4.5 h [12]. However, this approach does not include a considerable number of patients who might have salvageable brain tissue despite arriving after the 4.5 h time window or due to the moderate accuracy of the time from onset MRI-based estimation [13, 14]. Another possible approach is based on CT perfusion or PWI/DWI-MRI imaging to identify patients with potentially salvageable brain tissue, regardless of time elapsed from the stroke onset. A recent EXTEND trial based on perfusional imaging approach showed that the use of alteplase between 4.5 and 9.0 h after stroke onset or at the time the patient awakening with stroke symptoms resulted in a higher percentage of patients with no or mild neurologic deficits compared to placebo patients [15]. Nevertheless, thrombolytic therapy is underused in WUS patients and has not been widely studied in everyday clinical practice, yet. We aimed to investigate the benefits in thrombolysed patients in terms of ischemic lesion volume and neurological deficit and to draw a comparison with non-treated patients in everyday clinical practice.

Materials and methods

We retrospectively analyzed clinical and imaging data of patients with acute ischemic stroke admitted to the Stroke Unit of the University Medical Hospital of Trieste (Italy) between November 2013 and December 2018. The patients included in the study showed acute focal neurologic symptoms compatible with ischemic stroke developed at morning awakening. All patients with acute ischemic stroke were admitted to our emergency department within 4 h from awakening. The Alberta Stroke Program Early CT Score (ASPECTS) was used to quantify the amount of ischemia on nonenhanced computed tomography (NECT). No age limit was applied. Both genders were included in the study sample. We excluded hemorrhagic stroke patients, ASPECTS ≤ 6, patients with thrombolysis treatment contraindications, patients who were eligible but refused the treatment, and stroke mimics. Stroke mimics were excluded by a complete diagnostic work-up including anamnestic details, clinical and instrumental evaluation of patients. In particular, MRI assessment was used to confirm the absence of ischemic lesion in stroke mimic cases.

All included patients underwent common neurologic stroke workup, stroke risk factors assessment, electrocardiography, and carotid ultrasound; in most cases, transthoracic echocardiography (some patients had transesophageal echocardiography) and Holter electrocardiography. All patients underwent an NECT at admission, while only a part of them underwented angio CT and CT perfusion. In all cases a follow-up NECT at 24 h was performed. The Trial of Org 1072 in Acute Stroke Treatment (TOAST) classification was adopted to classify stroke etiology, lesion size, and type [16]. Symptomatic hemorrhage (sICH) was defined according to the definition of ECASS-3—European–Australasian Cooperative Acute Stroke Study 3 [17].

The following data of included patients were collected: (1) demographic details (age and sex); (2) stroke risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, obesity, ischemic cardiopathy, and atrial fibrillation); (3) National Institutes of Health Stroke Scale (NIHSS) score at baseline; (4) premorbid mRS; (5) NIHSS score on the 7th day or before in case of discharge; (6) mRS at discharge; (7) intra-hospital mortality; (8) length of hospitalization; (9) non enhanced CT (ASPECT Score); (10) lesion side; (11) follow-up non enhanced CT; (12) intracerebral hemorrage (ICH); (13) symptomatic intracerebral hemorrage (sICH); (14) stroke etiology by TOAST classification (15); stroke syndrome by Bamford classification; (16) rTPA and mechanical endovascular treatment (EVT); (17) time last known well-admission; and (18) symptom recognition–admission.

The included patients over the entire study period were divided into two subgroups: rTPA and non-rTPA groups. The rTPA group includes WUS patients who underwent rTPA treatment after fulfillment of eligibility criteria defined by the new standardized protocol for diagnosis and treatment of acute stroke of the Trieste University Hospital introduced in March 2016. Thanks to the advanced multiparametric CT assessment, the new rTPA protocol includes WUS patients who arrived before 4 h from awakening with ASPECTS > 6 or/and ischemic penumbra $> 50\%$ of ischemic tissue on CTP and current inclusion clinical criteria for administration rTPA. Patients eligible for thrombolysis were treated with intravenous rtPA (0.9 mg/kg of body weight, maximum of 90 mg, infused over 60 min with 10% of the total dose administered as an initial intravenous bolus over 1 min). The non-rTPA group encompassed the non-treated patients, admitted before the introduction of the new treatment protocol, who would fulfill the aforementioned rTPA eligibility in terms of clinical criteria and ASPECTS > 6. We investigated the differences between ischemic lesion volumes on follow-up NECT in the two groups. CT imaging was performed with one of the latest generation CT (Brilliance iCT 256 slices; Philips Medical Systems, Best, Netherlands) at the Radiology Department of the University Medical Hospital of Trieste (Italy). Non-enhanced CT was acquired with 120 kV, 400–450 mAs and reconstructed at 0.5 mm slice thickness. Ischemic lesion volume was calculated for all patients by a semiautomatic algorithm for segmentation, implemented in MATLAB (MathWorks, Natick, MA, USA), based on seed-based region growing algorithm, and with the possibility of additional manual outlining. The results of this semiautomatic process were checked by two independent neurologists blinded for the treatment. Disagreements were resolved with the consultancy of a third neurologist. For the differences

in functional outcome between treated and non-treated patients to be observed, we have evaluated the following parameters: Ischemic Lesion Volume at follow-up NECT, mortality rate, sICH, NIHSS determined at 7 days or—if discharged earlier—at discharge, and mRS at discharge, as well as ΔNIHSS calculated as percentage of NIHSS decreased from admission to discharge.

Statistical analysis

We performed all statistical analyses using SPSS Statistics 23 (IBM, Armonk/NY, USA). Kolmogorov–Smirnov test was used to evaluate the normal distribution of variables. Continuous variables with a normal distribution are presented as mean and standard deviations (SDs), those with a skewed distribution as median and interquartile ranges (IQRs) indicating the first and third quartiles, and categorical variables as counts and percentages (%). Subgroups were defined based on the administration of thrombolytic therapy. Differences between groups were tested with Student's *t* test for normally distributed continuous variables, Mann–Whitney *U* test for skewed variables, and Pearson's Chi square for categorical variables. To determine factors associated with NIHSS at 7 days and ischemic lesion volume calculated on follow-up NECT, multivariable linear regressions were performed. In particular, variables associated with *p* values <0.10 at univariate analysis were selected as candidate factors linear model. Results are presented as β, *B,* and 95% confidence intervals (95% CI). A value of $p<0.05$ was considered as significant.

Results

During the study period, 1935 patients with acute ischemic stroke were admitted to our Stroke Unit: 876 admitted before the introduction of new diagnostic and treatment stroke protocol and 1059 after protocol; out of them 107 (12.2%) and 110 (10.4%) suffered from WUS, respectively. Finally, 75 out of 107 WUS patients admitted before the introduction of protocol would have been eligible for rtPA treatment and, therefore, were included in non-rTPA group, while 74 of 110 patients admitted after the introduction of the protocol were eligible and underwent rTPA and were, therefore, included in interventional rTPA group.

Patients' demographics and stroke characteristics

The baseline clinical and radiological characteristics, as well as risk factors of WUS patients are presented in Table 1. Age was found significantly different between groups, with rTPA patients being younger than non-rTPA group (73 ± 1 years vs 79 ± 10 years, respectively) ($p=0.001$). Moreover, last known well to admission time (LKW-Adm) (527 min, 383–702 vs 684 min, 555–848, respectively) and symptoms to admission time (symptoms-Adm) (95 min, 64–126 vs 114 min, 63–216, respectively) were both shorter in the rTPA than in the non-rTPA group ($p=0.000$ and $p=0.045$, respectively). A significant difference was found in the stroke subtypes according to Bamford classification ($p=0.048$), while a significant smaller prevalence of HTN (72% vs 88%, $p=0.013$), DM (20% vs 35%, $p=0.049$), and AF (24% vs 53%, $p=0.000$) was found in the rTPA group compared to the non-rTPA group. No significant difference was found for sex, ASPECTS, NIHSS at baseline, anamnestic mRS, side of the lesion and TOAST classification, as well for other risk factors.

Stroke outcomes

Between the two groups, a significant difference was observed for the NIHSS at 7 days from admission, with smaller values observed in the rTPA group (1, 0–4) compared to the non-rTPA (3, 1–9) ($p=0.015$), that was still significant when the outcome was expressed as the difference between baseline and score at 7 days in absolute values ($p=0.013$) or percentage of improvement ($p=0.002$). A trend was present for a higher prevalence of mRS 0–2 in the rTPA group compared to the non-rTPA (54% vs 39%, $p=0.060$). No significant difference was found for the location of the lesion, although a higher prevalence of cerebellar lesions was found in the rTPA group compared to the non-rTPA (11% vs 1%, $p=0.029$). A reduced volume was measured on the follow-up NECT for patients treated with the rTPA (1 mL, 0–8) compared to the non-rTPA patients (10 mL, 0–40) ($p=0.000$). In addition, length of stay was shorter in the rTPA group (10 days, 6–18) than in the non-rTPA (15 days, 10–22) ($p=0.008$). No difference was observed for the mortality or prevalence of ICH and sICH. Stroke outcomes are summarized in Table 2.

Predictors of good outcomes

Univariate regression analysis suggested potential associations between NIHSS at 7 days and factors such as age, AF, NIHSS at baseline, anamnestic mRS, ASPECTS, rTPA treatment, and stroke subtypes. When these variables were included in the multivariate analysis, only NIHSS at baseline (β: 0.699, $p=0.000$) and rTPA (β: -0.141, $p=0.022$) remained significant predictors of NIHSS at 7 days (Table 3). When ischemic lesion volume on follow-up NECT was chosen as the dependent variable, AF, NIHSS at baseline, rTPA treatment, and stroke subtypes were found associated in the univariate analysis. Nevertheless, the multivariate analysis showed that only NIHSS at baseline (β: 0.568, $p=0.000$) and rTPA (β: -0.154, $p=0.041$) remained significant (Table 4).

Table 1 Participants' demographics and clinical characteristics at baseline in rTPa treated ($n=74$) and non-rTPA treated ($n=75$) wake-up stroke patients

Personal characteristics	rTPA $n=74$	non-rTPA $n=75$	Sig.
Age (years)	73 ± 13	79 ± 10	**0.001**
Females [*n* (%)]	44 (59)	36 (48)	0.161
Last time seen well-admission (min)	527 (383–702)	684 (555–848)	**0.000**
Symptom recognition-admission (min)	95 (64–126)	114 (63–216)	**0.045**
ASPECTS	10 (10–10)	10 (9–10)	0.194
NIHSS at baseline	6 (4–13)	7 (3–16)	0.980
Premorbid mRS	0 (0–0)	0 (0–0)	0.089
EVT [*n* (%)]	8 (11)	N/A	N/A
Left side of the lesion [*n* (%)]	44 (60)	41 (55)	0.490
Bamford stroke subtypes [*n* (%)]			**0.048**
TACI	21 (28)	26 (35)	0.409
PACI	30 (41)	26 (35)	0.459
LACI	8 (11)	17 (22)	0.052
POCI	15 (20)	6 (8)	**0.031**
TOAST classification [*n* (%)]			0.090
Atherothrombotic	19 (26)	8 (11)	**0.017**
Lacunar	8 (11)	8 (11)	0.997
Cardioembolic	18 (24)	29 (39)	0.059
Cryptogenic	29 (39)	29 (38)	0.948
Other cause	0 (0)	1 (1)	0.999
HTN [*n* (%)]	53 (72)	66 (88)	**0.013**
DM [*n* (%)]	15 (20)	26 (35)	**0.049**
Dislipidemia [*n* (%)]	47 (64)	47 (63)	0.565
Smoking [*n* (%)]	15 (20)	21 (25)	0.489
Obesity [*n* (%)]	7 (10)	13 (17)	0.168
AF [*n* (%)]	18 (24)	40 (53)	**0.000**
IC [*n* (%)]	15 (20)	22 (29)	0.217

Data are presented as means ± SD, medians (IQR) and frequencies

Participants' reported age (years), sex (females, %), time between last time seen well and admission (min), time between stroke symptom recognition and admission (min), ASPECTS, NIHSS at baseline, premorbid mRS, side of the ischemic lesion (left, %), Bamford stroke subtypes (%) (*TACI* total anterior circulation infarct, *PACI* partial anterior circulation infarct, *LACI* lacunar stroke, *POCI* posterior circulation infarct), TOAST classification (%), history of hypertension (HTN, %), diabetes (DM, %), dislipidemia (%), smoking (%), obesity (%), atrial fibrillation (AF, %), ischemic cardiomyopathy (IC, %). Results are summarized for patients treated with thrombolytic therapy (rTPA) and non-treated patients (non-rTPA). Significance value (Sig.) for intergroup comparison. Bold values for $p<0.05$

N/A not applicable

Discussion

A considerable number of acute ischemic stroke patients experienced stroke occurring during sleep. Although there is growing evidence for extending the time window for IV rtPA, thrombolytic therapy in WUS patients is underused in everyday clinical practice and as a standard of care. Indeed, the 2018 stroke guidelines put out by the AHA do not recommend administering IV rtPA beyond 4.5 h for any ischemic strokes, including wake-up strokes, despite advanced imaging [18]. The main finding of this study is that intravenous thrombolysis significantly reduces ischemic lesion volume and neurological deficit in WUS, without incrementing the risk in terms of intracranial hemorrhages and in-hospital mortality.

The results of this study showed that ischemic lesion volumes measured on follow-up NECT were significantly lower in rTPA group compared to the non-rTPA group (median 1 ml vs 10 ml, respectively), with both groups showing similar ASPECTS and NIHSS at admission. Figure 1 shows two different exemplificative cases of patients admitted to our stroke unit with an acute ischemic stroke at wake-up with similar age, NIHSS, mRS, ASPECTS at admission and resulting in two different functional outcomes and ischemic infarct lesion at follow-up NECT. Neurological deficit at presentation of acute ischemic stroke in terms of NIHSS

Table 2 Clinical outcomes at 7 days and at discharge after admission in rTPA treated ($n=74$) and non-rTPA-treated ($n=75$) wake-up stroke patients

Clinical outcomes	rTPA $n=74$	non-rTPA $n=75$	Sig.
NIHSS at 7 days	1 (0–4)	3 (1–9)	**0.015**
Δ NIHSS	4 (2–6)	3 (1–6)	**0.013**
Δ NIHSS percent	70 (43–100)	50 (30–68)	**0.002**
mRS at discharge 0–2 [*n* (%)]	40 (54)	29 (39)	0.060
mRS at discharge 0–1 [*n* (%)]	32 (42)	23 (31)	0.154
Location of the lesion [*n* (%)]			
Occipital	5 (7)	6 (8)	0.737
Temporal	14 (19)	17 (23)	0.517
Parietal	16 (22)	24 (32)	0.126
Frontal	23 (31)	24 (32)	0.817
Basal ganglia	16 (22)	24 (32)	0.126
Brainstem and cerebellum	7 (11)	1 (1)	**0.029**
Follow-up NECT (mL)	1 (0–8)	10 (0–40)	**0.000**
Length of stay (days)	10 (6–18)	15 (10–22)	**0.008**
Mortality [*n* (%)]	5 (7)	6 (8)	0.754
ICH [*n* (%)]	8 (11)	5 (7)	0.370
sICH	1 (2)		0.992

Data are presented as medians (IQR) and frequencies

Participants' NIHSS at 7 days from admission, difference between NIHSS at admission and NIHSS at 7 days (Δ NIHSS), percent of improvement between NIHSS at baseline and NIHSS at 7 days (Δ NIHSS percent), mRS between 0–2 (%) and 0–1 (%), location, where the lesion occurred (%), volume of the follow-up NECT (mL), length of stay (days), mortality (%), intracerebral haemorrhage (ICH, %) and symptomatic intracerebral haemorrhage (sICH, %). Results are summarized for patients treated with thrombolytic therapy (rTPA) and non-treated patients (non-rTPA). Significance value (Sig.) for intergroup comparison. Bold values for $p<0.05$

Table 3 Linear multivariate regression for NIHSS at 7 days after admission

Variable	*β*	*B*	NIHSS at 7 days 95% CI	Sig.
Age (years)	0.066	0.032	− 0.030 to 0.094	0.307
AF	− 0.038	− 0.457	− 2.062 to 1.148	0.574
NIHSS at baseline	0.699	0.615	0.494 to 0.736	**0.000**
Premorbid mRS	0.027	0.195	− 0.647 to 1.038	0.647
ASPECTS	− 0.060	− 0.302	− 0.958 to 0.354	0.364
rTPA	− 0.141	− 1.636	− 3.028 to − 0.244	**0.022**
Bamford stroke subtypes	− 0.052	− 0.299	− 1.067 to 0.470	0.443

Multivariate analysis for NIHSS at 7 days from admission. Variables found significant in the univariate analysis. Age (years), atrial fibrillation (AF), NIHSS at baseline, premorbid mRS, ASPECTS, treatment with thrombolytic therapy (rTPA), Bamford stroke subtypes classification. Significance (Sig.) for multivariate analysis. Bold values for $p<0.05$

has been found to be correlated with hypoperfused volume at admission [19]. The preservation of the brain tissue, i.e., minor ischemic volume of final lesion after an acute ischemic event may be a good neuropathological base for a better motor and cognitive recovery [20]. A previous study found that the infarct volume measured by CT or MRI within 72 h from ischemic stroke onset is an independent predictor of functional outcome at 90 days [21]. NIHSS at 7 days was significantly lower in treated WUS patients compared to the non-treated (median 1 vs 3, respectively), while proportion of mRS 0–2 was higher although non statistically significant (54% vs 39%, respectively). In addition, the recovery in terms of NIHSS reduction from admission to the 7th day was also significantly higher in the rTPA group compared to the non-rTPA (70% vs 50%, respectively).

Recent wake up and extend trials, performed in well selected patients, also reported better functional outcome in terms of mRS and NIHSS [12, 15]. Wake-up trial demonstrated the benefit of rTPA in WUS patients with DWI/FLAIR MRI pattern suggestive of stroke with an onset of less than 4.5 h. The results of EXTEND trial, using PWI/DWI-MRI and CT perfusion, showed that the rtPA in selected patients resulted in higher number of patients with no or minor neurologic deficits [15]. The DWI/FLAIR-based selection used in wake-up trial identifies around 62% of patients who are within the 0–4.5 h time window [13] and such approach excludes patients who might have salvageable brain tissue, despite arriving at more than 4.5 h after stroke onset. In EXTEND trial, about 65% of included patients were WUS; in these patients stroke onset was estimated as the midpoint of sleep and underwent randomization if they were within 9 h of the estimated time of onset [15]. Our results showed the efficacy and safety of rTPA therapy in WUS patients selected with NECT and/or CTP assessment in larger time window (last known well-admission: median 527 min; range 280–1374) reflecting everyday clinical reality and, therefore, increasing the generalizability of the benefit of rTPA in these patients. A recent real-life study performed on 70 rTPA and mechanical thrombectomy-treated patients admitted in an extended window beyond 4.5 h from last seen well (60% of included patients were WUS) showed that reperfusion therapies were safe (sICH 5.7%; in-hospital mortality 11.4%) and effective (median NIHSS at discharge 3; mRS at discharge 0–1: 18%; 0–2: 39%) in CTP selected patients [22]. In our study, we observed a slightly better outcome in terms of discharge NIHSS, mRS and in-hospital mortality, and sICH, probably reflecting that WUS mostly occurs in the early morning hours leading to lower onset to admission time.

These considerations are important considering that about 8–28% of stroke patients notice their stroke symptoms upon awakening [1–3]. In our cohort, during the study period, 11.2% of ischemic stroke admissions were WUS. A recent

Table 4 Linear multivariate regression for follow-up NECT

Variable	β	B	Follow-up NECT 95% CI	Sig.
AF	− 0.006	− 0.829	− 20.706 to 19.048	0.934
NIHSS at baseline	0.568	5.062	3.585 to 6.539	**0.000**
rTPA	− 0.154	− 19.278	− 37.761 to − 0–794	**0.041**
Bamford stroke subtypes	0.063	3.854	− 6.125 to 13.8.32	0.446

Multivariate analysis for follow-up NECT volume. Variables found significant in the univariate analysis. Atrial fibrillation (AF), NIHSS at baseline, treatment with thrombolytic therapy (rTPA), Bamford stroke subtypes classification. Significance (Sig.) for multivariate analysis. Bold values for $p < 0.05$

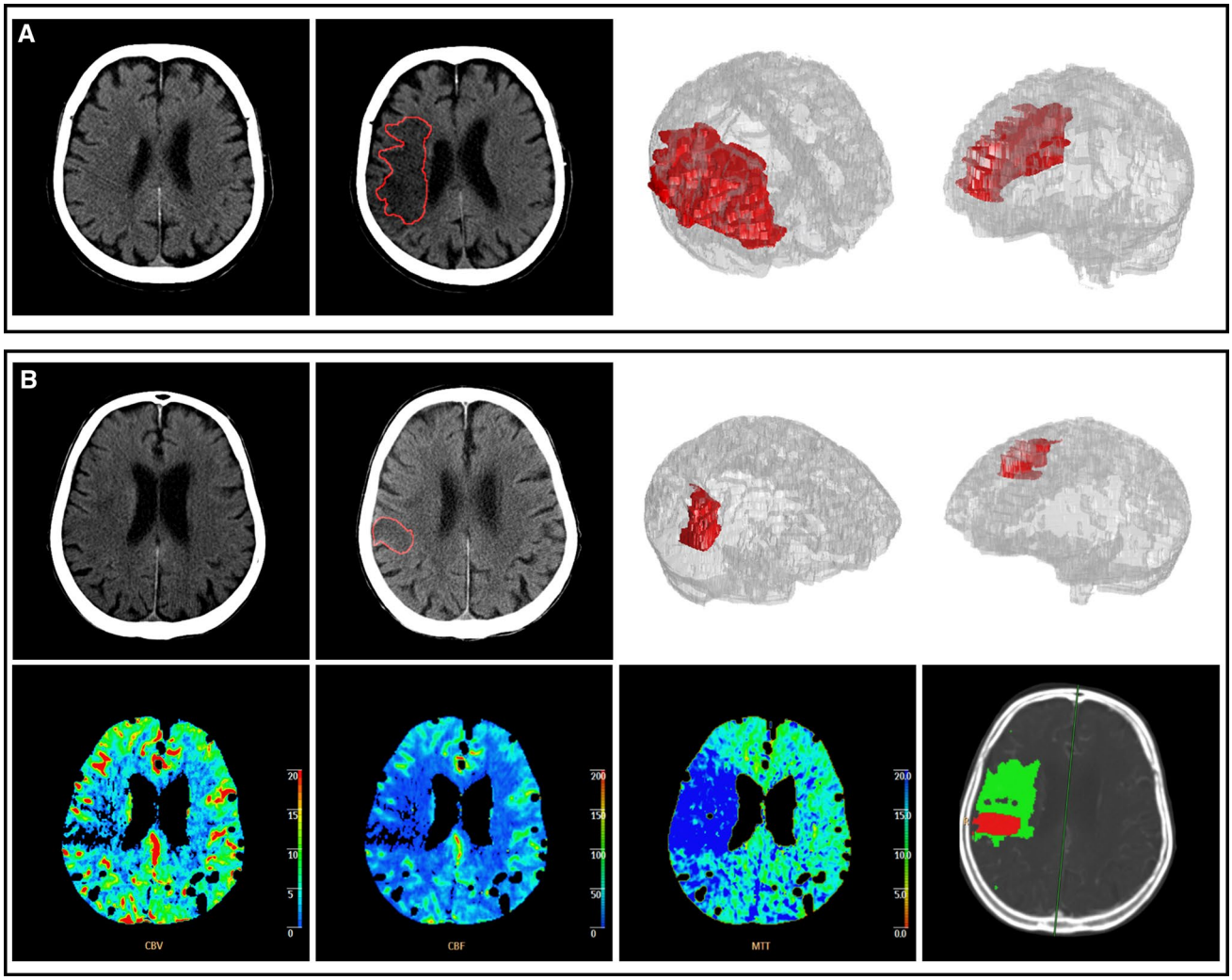

Fig. 1 **a** Non-thrombolised wake-up stroke patient: female, 85 years, ASPECTS = 10, right M2-occlusion, PACI, NIHSS at admission = 16, premorbid mRS = 0, NIHSS at 7 days = 16, mRS at discharge = 5. From left to right: NECT at admission, follow-up NECT with delineated ischemic lesion, 3D reconstruction of ischemic lesion on follow-up NECT (red). **b** Thrombolised wake-up stroke patient: female, 84 years, ASPECTS = 9, right M2-occlusion, PACI, NIHSS at admission = 16, premorbid mRS = 0, NIHSS at 7 days = 4, mRS at discharge = 2. Top panel—from left to right: NECT at admission, follow-up NECT with delineated ischemic lesion, 3D reconstruction of ischemic lesion on follow-up NECT (red). Bottom panel—from left to right: CTP calculated CBV, CBF, and MTT maps, and CTP core-penumbra color map with estimated core area (145% of the contralateral healthy area and CBV < 2.0 mL/100 g) and penumbra area (145% of the contralateral healthy area and CBV > 2.0 mL/100 g), highlighted in red and green, respectively

study showed that there is a 55% higher risk of having a stroke during the morning hours between 6:00 am and noon [23]. Increased blood pressure, heart rate, renin–angiotensin–aldosterone activity, plasma cortisol levels, platelet aggregation, Lp(a), fibrinogen, prothrombotic factors, and increased sympathetic activity during the early morning may support the hypothesis of stroke onset in this period, thus making WUS eligible for acute treatment [9–11]. Neuroimaging can play a pivotal role in patient selection for both intravenous and intra-arterial treatments of acute ischemic stroke [24, 25]. Recent studies and trials used different neuroimaging techniques and neuroradiological parameters as eligibility criteria for rTPA treatment in WUS [4, 13, 15, 26–29].

The WAKE-UP trial provided evidence for a clinical benefit and safety of MRI-guided DWI-FLAIR mismatch-based rTPA eligibility [13]. EXTEND trial, based on CT perfusion or PWI-DWI-MRI-imaging techniques with the use of a research version of RAPID software has demonstrated rTPA treatment efficacy in patients with favorable perfusion-imaging profile between 4.5 and 9 h after stroke onset or at awakening [15]. Advanced neuroimaging, especially MRI, may limit the generalizability of the decision-making approach, as it is not widely available as CT imaging. In our study, treatment decision-making was based on ASPECTS > 6 on NECT at admission performed in all included patients and/or penumbra-core mismatch > 50% on CTP performed in 41% of 149 included participants. Our results, obtained by CT-based selection, are complementary to those obtained in a randomized controlled trial setting, to report the real-world experience with applying rtPA to patients with WUS. Finally, multivariate analysis showed that NIHSS at baseline and rTPA treatment are significant predictors of good outcome both in terms of NIHSS at 7 day and ischemic lesion volume on follow-up NECT. Similar results for multivariate analysis of functional outcome were reported in a recent Austrian national registry study in which rTPA therapy was significantly associated with NIHSS ≥ 4 neurological improvement [27] and in an observational study in which rtPA, age, baseline NIHSS were predictors of a mRS of 0–2 at 90 days [30].

Several limitations are noted in this study. The sample size is modest with 149 included patients; another limitation is the retrospective character of this study with the potential effects of unmeasured confounders. Only 41% of patients was assessed with CTP at admission. As the follow-up at 3 months is not mandatory, mRS was collected at discharge. As many as eight rTPA patients were treated with endovascular treatment, too. Although this percentage was rather low, the outcome of these eight patients may have been modified by this intervention.

In conclusion, the results of this single-center study suggest that thrombolysis in WUS patients selected with NECT and/or CTP results in reduced ischemic infarct volume on follow-up NECT, better functional outcome and it does not increase the risk of intracranial hemorrhages and in-hospital mortality. These findings may contribute to a greater diffusion and the generalizability of rTPA in WUS in everyday clinical scenarios.

Acknowledgements M. Ajčević is supported by AIRAlzh Onlus-(ANCC-COOP). The authors would like to thank Matteo di Franza for editorial and proofreading assistance.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standards The research was conducted according to the principles of the Declaration of Helsinki. All participants released their informed consent for treatment of clinical data after all procedures had been fully explained, as for standard institutional procedure. This retrospective study was approved by the Local Ethics Committee CEUR (Comitato Etico Unico Regionale, FVG, Italy) with approval number 115/2018.

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